NUMBER 80 May 2013

# CODE OF PRACTICE REVIEW

PMCPA | 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 ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.**

## COMPLAINTS IN 2012 DOWN ON 2011 BUT THE SAME NUMBER OF CASES TO BE CONSIDERED

In 2012 the PMCPA received 78 complaints as compared with 84 in 2011. There were 86 complaints in 2010, 92 complaints in 2009, 112 complaints in 2008 and 127 complaints in 2007.

There were 84 cases to be considered in 2012, the same as in 2011. The number of cases usually differs from the number of complaints because some complaints involve more than one company and others do not become cases at all, often because they do not show that there may have been a breach of the Code.

The number of complaints from health professionals in 2012 (21) was more than the number from pharmaceutical companies (both members and non-members of the ABPI) (16). In addition there were 11 complaints from anonymous health professionals. The more complex cases considered by the Authority are generally inter-company complaints which often raise a number of issues.

Five complaints were made by members of the public and three by employees/ex-employees.

There were 12 other anonymous complaints in addition to the 11 from anonymous health professionals. Four were from anonymous employees.

The remaining 10 complaints were nominally made by the Director and arose from voluntary admissions by companies and alleged breaches of undertakings.

## AMENDMENT TO THE SECOND 2012 EDITION OF THE CODE

Proposals to amend Clause 16 of the ABPI Code of Practice for the Pharmaceutical Industry Second 2012 Edition were agreed by the ABPI on 25 April 2013. The changes to the representatives' examinations will come into operation on 1 July 2013. During the period 1 July to 31 October there will be a transition period for the ABPI examinations such that it will not be a breach of Clause 16.3 to fail to comply with the newly introduced requirements in that clause. A new edition of the Code will not be printed. An addendum is available from the PMCPA website for use with the Second 2012 Edition.

There will be a new edition of the Code in 2014.

## NEW DEPUTY SECRETARY APPOINTED

The ABPI Board of Management has appointed Tannyth Cox to be the new Deputy Secretary to the Authority. Tannyth is registered and worked as a pharmacist in South Africa before coming to the UK to work in medical information for a pharmaceutical company. Her most recent role, as scientific affairs advisor at Actelion, includes providing expert advice and training on the Code as well as reviewing promotional materials. Tannyth joins the Authority in June. We congratulate Tannyth on her appointment and look forward to working with her and to her contribution to the work of the Authority.

## UPDATED ADVICE ON ADVISORY BOARDS

The arrangements for advisory board meetings are often the subject of enquiries for informal advice. They are also discussed with companies when audits are carried out by the Authority. In the light of this the Authority thought it would be helpful to update its guidance 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. Advisory boards should only be held to enable companies to answer legitimate business questions to which they do not already know the answer. The arrangements for such meetings have to comply with the Code.

*Continued overleaf...*

## CODE OF PRACTICE TRAINING

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

These full day seminars offer 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:

Tuesday, 23 July

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

*For further information regarding any of the above, please contact Nora Alexander for details (020 7747 1443 or nalexander@pmcpa.org.uk).*

## HOW TO CONTACT THE AUTHORITY

Our address is:
Prescription Medicines Code of Practice Authority
7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

www.pmcpa.org.uk

Telephone: 020 7747 8880
Facsimile: 020 7747 8881

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

Direct lines can be used to contact members of the Authority.
Heather Simmonds: 020 7747 1438
Etta Logan: 020 7747 1405
Jane Landles: 020 7747 1415

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

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

## UPDATED ADVICE ON ADVISORY BOARDS (Continued from cover)

Advisory board meetings need to meet the requirements for meetings as set out in Clause 19 of the Code including the requirements that the meeting is held in an appropriate venue conducive to the business purpose of the meeting and that hospitality is secondary to that purpose and of an appropriate standard.

To be considered a legitimate advisory board the choice and number of participants 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 participants should be limited so as to allow active participation by all and should not be driven by the invitees' willingness to attend. The agenda should allow adequate time for discussion. The number of meetings and the number of participants at each should be dictated by need ie both should be strictly limited to no more than the number required to achieve the stated objective. Multiple advisory boards on the same topic should be avoided unless a clear need can be demonstrated. Companies should determine if and when advisory board meetings are required; advisory boards should never be held in response to participants' willingness to discuss issues. Invitations to participate in an advisory board meeting should state the purpose of the meeting, the expected advisory role and the amount of work to be undertaken.

The content of advisory board meetings should relate solely to the matter in hand. Discussion of clinical data about a particular medicine should only take place at an advisory board if such discussion is essential to meet the stated objective. To do otherwise might risk the meeting being viewed as disguised promotion for that medicine or promotion of an unlicensed medicine or indication.

If an honorarium is offered it should be made 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. The payment of advisory board members must be declared in accordance with Clause 20.

**CASE AUTH/2528/8/12**

# GENZYME v SHIRE

## VPRIV press release

**Genzyme Therapeutics alleged that a press release issued by Shire Pharmaceuticals, entitled 'Shire's VPRIV (velaglucerase alfa for injection) Shows Significant Improvement in Gaucher-Related Bone Disease', contained disparaging comparisons with its product Cerezyme (imiglucerase) that were not accurate, balanced, fair or based on up-to-date information. They were based on an analysis of exploratory endpoints in a small subgroup using treatment arms that had significant and relevant differences at baseline. Put simply, this analysis was not designed properly to assess changes in bone mineral density (BMD). The press release also selectively focused on some data and endpoints, but not others.**

**Genzyme noted that Shire had placed the press release on its global website and had also provided a copy of it through its UK public relations agents to a UK patient group.**

**The detailed response from Shire is given below.**

**Genzyme noted that the comparison of changes in BMD for patients taking VPRIV and Cerezyme was based on a number of subgroup retrospective analyses of data collected from the original 2008-2009 Phase III study. BMD was not a primary or secondary endpoint of the study; rather, it was measured as an 'exploratory' endpoint. As an 'exploratory' endpoint, BMD Z-scores could not be used as evidence of clinical superiority. Although a statement that the evaluation of BMD was exploratory was in the fifth paragraph of the press release, the press release was still unbalanced and unfair.**

**The press release misleadingly implied that the statistical significance and comparative/superiority efficacy claims were properly derived from an analysis of a prospectively defined primary endpoint.**

**Genzyme alleged that the press release selectively used mean and median data to convey the message that VPRIV improved BMD more than Cerezyme. Specifically, the press release only included information on the median baseline Z-scores and not the mean or average baseline, even though when describing improvements in BMD, the press release switched to mean changes from baseline. While Shire argued that the median allowed for a fair presentation of the central value and was not influenced by outlying values (unlike presentation of the mean), this argument was not credible when the press release subsequently switched to mean changes from baseline. In addition, the median baseline Z-scores were dramatically closer than the mean baseline Z-scores. As a result, the press release conveyed a misleading message that the patients' BMD levels were more comparable than they actually were.**

**Genzyme noted that had Shire adjusted properly for baseline differences, patients taking Cerezyme might have demonstrated a greater percentage improvement in BMD than patients taking VPRIV. As such, the press release made inaccurate and misleading superiority claims.**

**Genzyme noted that although Shire acknowledged the imbalances with baseline lumbar spine Z-scores, it asserted that the results were robust because it had obtained similar results after adjusting for this difference. However, the results after adjusting for this difference were from a 'within-group' analysis, which could not support comparative/superiority efficacy claims. Thus, failure to disclose in the press release that no conclusion regarding group-to-group comparisons could be made based on the data from the study was misleading.**

**Genzyme noted that the title of the press release made the general conclusion that VPRIV showed significant improvement in 'Gaucher-Related Bone Disease'. However, the body of the press release only reported the data relating to BMD measurements in the lumbar spine. For example, Shire did not include femoral neck BMD Z-scores because VPRIV was not shown to have a positive effect on femoral BMD after 9 months. Thus, the BMD Z-scores were presented selectively and presented an inaccurate and misleading efficacy claim that VPRIV improved BMD more than Cerezyme.**

**Genzyme, however, alleged that the press release went beyond reporting the scientific data from the study at issue and made comparative/superiority claims. In addition, the BMD data presented in the press release did not constitute an up-to-date evaluation of all the evidence because it did not include data that showed that Cerezyme had statistically significant results on bone disease, including BMD measurements. Genzyme alleged that the analysis in the press release was not accurate, balanced, fair, objective, unambiguous, or based on an up-to-date evaluation of all the evidence in breach of the Code.**

**With regard to whether the press release came within the scope of the Code, the Panel noted that it had been issued by Shire plc, in Switzerland and published on the global, but not the UK, website. There was no reference to the use or availability of VPRIV in the UK although UK contact telephone numbers were provided. Readers were advised to consult local prescribing information and told where to find the US prescribing information. The Panel noted Shire's submission that the press release was not directed to a specifically UK audience. However, the Panel further noted that the press release had been sent to, *inter alia*, a UK patient organisation and therefore considered that the content of the**

**press release came within the scope of the Code and had to comply with it.**

**The Panel noted that the title of the press release was 'Shire's VPRIV (velaglucerase alfa injection) Shows Significant Improvement in Gaucher-Related Bone Disease'. Below this, in slightly smaller text, was the prominent subheading 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density'. The press release then detailed the results of a head-to-head Phase III clinical study (HGT-GCB-039) and follow on extension trial (HGT-GCB-044) with VPRIV in relation to lumbar spine BMD, stating, *inter alia*, that clinically and statistically significant improvement from baseline in mean lumbar spine Z-score was seen at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme. The Panel disagreed with Shire's repeated assertions that no comparative or superiority claims were made.**

**The Panel noted from the entry on ClinicalTrials.gov for the trial HGT-GCB-039 that the title of the study was 'Study of Gene-Activated Human Glucocerebrosidase (GA-GCB) ERT Compared With Imiglucerase in Type I Gaucher Disease'. Under the section 'Purpose' was the statement 'The purpose of this non-inferiority study is to evaluate the efficacy and safety of GA-GCB (velaglucerase alfa) administered every other week in comparison to imiglucerase in treatment naïve patients with type 1 Gaucher disease'. The primary outcome measures were mean change from baseline to month 9 in haemoglobin concentration for each treatment group and the secondary outcome measures as change from baseline to month 9 in platelet counts; change from baseline to month 9 in normalized liver volume; change from baseline to month 9 in normalized spleen volume; change from baseline to month 9 in plasma chitotriosidase; change from baseline to month 9 in plasma chemokine (C-C motif) ligand 18; number of patients who developed antibodies to treatment and a comparison of GA-GCB and imiglucerase on the earliest time to respond as assessed via haemoglobin concentration.**

**The entry on ClinicalTrials.gov for the trial HGT-GCB-044 noted that the title of the study was 'An Open-Label Extension Study of GA-GCB ERT in Patients With Type 1 Gaucher Disease'. The purpose of the study was to evaluate the long-term safety of every other week dosing of VPRIV intravenously in patients with type 1 Gaucher disease, the primary outcome measure was the evaluation of safety and the secondary outcome measures were the evaluation of haematological parameters and organomegaly.**

**The Panel noted that the poster (Zimran *et al* 2012), upon which the press release was based, was entitled 'Bone mineral density response to enzyme replacement therapy over 2 years in adults with type 1 Gaucher disease'. It explained that the study HGT-GCB-039 was a Phase III, randomized, parallel-group trial in patients with type 1 Gaucher disease; one group was allocated VPRIV (n=13) and the other Cerezyme (n=11) therapy for 9 months. In the extension study (HGT-GCB-044), which was ongoing, those patients taking VPRIV continued to do so and those taking Cerezyme were switched to VPRIV. BMD was measured for the lumbar spine and femoral neck at baseline, 9 and 24 months relative to baseline. The statistical analysis section of the poster referred to the BMD assessment being pre-specified as exploratory and thus there were no pre-specified hypotheses. The poster went on to state that because there were no specific bone-related inclusion or exclusion criteria in the protocols for the studies and the randomization was not stratified by BMD, there were imbalances between the two treatment arms at baseline such that the mean lumbar spine BMD Z-score in the VPRIV group was -1.56 and -0.57 in the Cerezyme group (although the press release referred to the more closely matched median baseline figures of -1.46 and -0.86, respectively). Additional analyses adjusting for baseline lumbar spine bone status were performed in patients with a baseline lumbar spine T-score <-1 (excluding patients with normal density) and in patients with a baseline lumbar spine Z-score <-1 but this reduced the number of patients in each treatment arm (VPRIV (n=9) and Cerezyme (n=4)). Although this additional analysis confirmed the lumbar spine BMD Z-score results in the wider patient group the Panel noted that there were only 4 patients in the Cerezyme group and more than double that in the VPRIV group.**

**The Panel noted that despite the limitations of the data noted above, the title and subheading of the press release as set out above was unequivocal. A further statement read 'Results from a head-to-head Phase III study (HGT-GCB-039) of VPRIV and Cerezyme, and follow-on extension trial (HGT-GCB-044) of VPRIV, demonstrate a statistically significant improvement in lumbar spine (LS) BMD in Gaucher patients starting at nine months of treatment with VPRIV (P<0.05)'. The only reference to BMD being evaluated as an exploratory endpoint was in a sentence in the fifth paragraph of the press release which detailed how BMD was measured.**

**The Panel did not accept Shire's submission that the press release made no comparative claims. The Panel was concerned that the press release was not clear that the extension study from which the BMD results were obtained was not a head-to-head study of VPRIV and Cerezyme; it gave a contrary impression in this regard. The extension study compared BMD results within each group to baseline. The press release was misleading on this point and a breach of the Code was ruled. This ruling was appealed by Shire. In addition, the Panel did not consider that it was sufficiently clear from the press release that BMD was a pre-specified exploratory endpoint. The only reference to this was towards the end of the press release and there was no explanation that no confirmatory clinical conclusions could be drawn from such an endpoint. In the opinion of the Panel the press release invited the reader to draw such conclusions. Exploratory endpoints could not be used as the basis for a robust comparison of medicines. The Panel**

**considered that the press release was misleading in that regard and ruled a breach of the Code. This ruling was appealed by Shire.**

**The Panel considered that the allegations about sample size and use of mean/median in relation to the changes in BMD were covered by its comments about the presentation of the BMD data in the press release. The Panel considered that overall the press release was not a fair reflection of the data. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the findings. A breach of the Code was ruled. This ruling was appealed by Shire.**

**The Panel noted Genzyme's allegation that the press release did not include the BMD Z-scores relating to the neck of the femoral bone. The press release stated that the femoral neck changes from baseline in both cohorts were not significant at either 9 or 24 months. The Panel noted its comments and ruling above in relation to BMD. However, and on balance, in relation to the very narrow ground alleged, the Panel did not consider that the press release was misleading solely because it failed to quantify the femoral neck BMD as alleged and thus no breach of the Code was ruled. This ruling was not appealed.**

**In considering the appeals noted above the Appeal Board noted the press release was based upon the poster presented at the European Working Group on Gaucher Disease (EWGGD) in Paris in June 2012 titled 'Bone Mineral Density Response to Enzyme Replacement Therapy Over 2 Years in Adults with Type 1 Gaucher Disease'. The Appeal Board noted from the statistical analysis section in the poster that 'As the assessment of BMD using DXA in the study protocols of HGT-GCB-39 and HGT-GCB-44 was pre-specified as exploratory, there were no pre-specified hypotheses'.**

**The Appeal Board did not accept Shire's submission that the press release made no comparative claims. The Appeal Board noted that the prominent subheading of the press release read 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months'. In addition, the fourth paragraph of the press release stated 'Results from a head-to-head Phase III Study (HGT-GCB-039) of VPRIV and Cerezyme, and follow-on extension trial (HGT-GCB-044) of VPRIV, demonstrate a statistically significant improvement in lumbar spine (LS) BMD in Gaucher patients starting at nine months of treatment with VPRIV ($p<0.05$)'. The Appeal Board considered that, overall, it was not clear that the extension trial (HGT-GCB-044) had compared BMD results for VPRIV and Cerezyme to baseline and was not a head-to-head, between group comparison of VPRIV and Cerezyme. The Appeal Board considered that this was misleading and it upheld the Panel's ruling of a breach of the Code. Shire's appeal on this point was unsuccessful.**

**The Appeal Board considered that the press release, in particular the bold title and prominent subheading, implied that confirmatory results had been presented. Only once in paragraph five towards the end of the press release did it state that 'BMD, evaluated as an exploratory endpoint in the Phase III and extension studies, …' and this was insufficient to negate the overall impression that confirmatory clinical conclusions could be drawn. The press release was not sufficiently clear. The Appeal Board considered that the press release was thus misleading and upheld the Panel's ruling of a breach of the Code. Shire's appeal on this point was unsuccessful.**

**The Appeal Board noted from the poster that because there were no specific bone-related inclusion or exclusion criteria in the protocols for the studies and the randomization was not stratified by BMD, there were imbalances between the two treatment arms at baseline. The mean lumbar spine BMD Z-score in the VPRIV group was -1.56 and -0.47 in the Cerezyme group (the press release presented median values of -1.46 and -0.86, respectively). In the group of patients who did not receive bisphosphonates 2/11 had normal bone in the lumbar spine in the VPRIV group compared with 4/8 in the Cerezyme group. The Appeal Board noted that the patient numbers had not been included in the press release and considered that it would have been helpful if they had been, especially given the small number of patients in the studies (VPRIV n=13, Cerezyme n=11 and after adjustments to exclude patients with a baseline lumbar spine Z score of <-1, VPRIV n=8 and Cerezyme n=4). The Appeal Board noted Shire's acknowledgment at the appeal that the observed effects might be caused by type II statistical errors. The Appeal Board considered that overall the press release had not provided sufficient information for the reader to assess what weight to attach to the findings. The press release was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of the Code. Shire's appeal on this point was unsuccessful.**

**Genzyme strongly disagreed with Shire's view that the press release contained no comparisons.**

**Specifically, it included a sub-headline which stated that, 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months' (emphasis added). Paragraph 5 described how the clinical study showed 'clinically and statistically significant improvement from baseline in mean [lumbar spine] Z-score … at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme' (emphasis added). Moreover, paragraph 5 also presented, in direct proximity, data from patients treated with VPRIV and patients treated with Cerezyme. It was indisputable that the totality of these claims conveyed the message that based on the data, VPRIV offered a clinical advantage over Cerezyme.**

**Genzyme alleged that the comparisons were misleading. Since the BMD analysis was exploratory, Shire's studies were not designed to be sufficiently powered for this analysis. In addition,**

**even assuming that the original study was sufficiently powered for this exploratory endpoint, the BMD analysis was based on a subgroup of a subgroup. Consequently, this retrospective BMD subgroup analysis was insufficiently powered to draw statistically significant conclusions.**

**Genzyme repeated its previous comments with regard to the differences in baseline BMD for the Cerezyme and VPRIV groups.**

**In addition, Genzyme alleged that the main data, the difference in mean changes from baseline in lumbar spine BMD Z-score of the two treatment groups was neither statistically valid nor reliable. The 95% confidence intervals covered a wide range of possible mean changes in BMD ie individual responses to the two medicines varied widely, and the distribution of these responses overlapped. Given that the confidence intervals for the VPRIV and Cerezyme patient groups contained a significant amount of overlap, it was likely that there was no statistical difference between the two groups. Thus it could not be concluded that the mean changes in BMD were different, as opposed to being a result of mere chance. In other words, given that there was no significant difference between the groups for the outcomes measured, no conclusion regarding comparative effectiveness or superiority could be drawn.**

**Genzyme alleged the press release was unbalanced to selectively present lumbar spine Z-scores. In addition, conclusions of product superiority based on exploratory endpoints must be adjusted for multiple endpoints in order to obtain a valid statistical significance. Even though the superiority claims made by the press release were based on multiple endpoints as well as an exploratory endpoint, the press release failed to disclose that this statistical adjustment was not made. Correcting for these multiple endpoints, a proper statistical analysis would not show improvement in VPRIV.**

**Genzyme alleged that, for the reasons above, the press release misleadingly suggested that this was a like-for-like comparison based on a prospectively designed study devised to evaluate BMD as a primary endpoint in breach of the Code.**

**The Panel considered that Shire's assertions that the press release contained no direct comparisons between VPRIV and Cerezyme and that no confirmatory claims were stated or implied were disingenuous. It noted its comments above in this regard. The original study from which baseline measurements of BMD were taken was a head-to-head non-inferiority study of VPRIV and Cerezyme in type 1 Gaucher disease, the primary endpoints of which were unrelated to BMD. The subheading of the press release stated that in a head-to-head trial between VPRIV and Cerezyme, only those treated with VPRIV experienced a statistically significant improvement in lumbar spine BMD at 9 months. The press release went on to state that a statistically significant improvement from baseline in mean lumbar Z-score was seen at 9 months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme.**

**The Panel noted each party's submission about baseline BMD measurements and sample size. It noted its general comment about the press release above. Given the exploratory nature of the BMD analysis it was self evident that the studies were not powered to provide confirmatory findings on BMD. The press release gave a contrary impression. Ultimately the allegations on this point were inextricably linked to the point above and the Panel considered that its ruling of a breach of the code applied equally here. This ruling was upheld by the Appeal Board following an appeal by Shire.**

**Genzyme alleged that to argue that the press release contained no comparative/superiority claim simply ignored the plain language of the document. Moreover, as described in detail above, this comparison was unbalanced, unfair, not based on an up-to-date evaluation of all the evidence and based upon unsound statistics. All these elements underscored the misleading nature of the comparative/superiority claims in the press release in breach of the Code.**

**The Panel noted its comments and rulings above about comparisons in the press release between VPRIV and Cerezyme in relation to BMD results. The Panel considered that the press release implied that the studies cited had produced robust confirmatory comparative data that VPRIV significantly improved lumbar spine BMD and that Cerezyme did not. This was not so. The data was such that no conclusive comparisons could be made. The comparison was misleading and a breach of the Code was ruled. This ruling was appealed by Shire.**

**The Appeal Board noted its comments and rulings above. The Appeal Board considered the press release, in particular the title and subheading, compared VPRIV with Cerezyme and implied that there was confirmatory evidence that VPRIV significantly improved lumbar spine BMD and that Cerezyme did not. The evidence, however, was insufficient to make such a comparison and the press release was misleading in this regard. The Appeal Board upheld the Panel's ruling of a breach of the Code. Shire's appeal on this point was unsuccessful.**

**Genzyme alleged that the press release was promotional and was intended for dissemination to patients and to the public in breach of the Code. The press release advertised a prescription only medicine to the public in breach of the Code.**

**The Panel considered that it was not unacceptable to make available information about prescription only medicines to patient organisations but its content and provision had to comply with the Code.**

**The Panel noted that Genzyme's allegation that the press release was promotional appeared to be based on the fact that a press release which contained information about a prescription only medicine was distributed to a patient organisation. On this narrow point, and given its comments above, the Panel did not consider that the press release was promotional and ruled no breach of the Code. This ruling was appealed by Genzyme.**

**The Appeal Board noted its rulings in above where it had ruled that the press release had made misleading claims about VPRIV, and VPRIV vs Cerezyme based on limited exploratory data. The Appeal Board noted that the press release had been widely circulated including to a patient organisation. The Appeal Board noted that the Code prohibited the advertisement of prescription only medicines to the public. The Appeal Board considered that the press release, although not an advertisement *per se*, did promote VPRIV and thus it ruled a breach of the Code. Genzyme's appeal on this point was successful.**

**The Panel noted that the Code required that information about prescription only medicines which was made available to the 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. Statements must not be made to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine.**

**The Panel noted its rulings above in relation to the misleading statements made about VPRIV in relation to BMD and considered that the press release had not presented information about VPRIV in a balanced way. The press release was likely to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. A breach of the Code was ruled. This ruling was upheld by the Appeal Board following an appeal by Shire.**

**Genzyme alleged that the press release disparaged Cerezyme as it contained a comparative/superiority claim that was not included in the underlying poster. Moreover, the scientific analysis upon which the claim was based was flawed as detailed above.**

**Whilst the Panel noted its ruling above in relation to the misleading comparisons between VPRIV and Cerezyme, on balance the Panel did not consider that such comparisons amounted to disparagement as alleged. The claims, although ruled above to be misleading, were so in relation to positive comments about VPRIV. There was no implication that Cerezyme was not effective in increasing BMD in Gaucher disease. No breach of the Code was ruled. This ruling was appealed by Genzyme.**

**The Appeal Board noted its rulings above. The press release made comparative claims that VPRIV had an advantage over Cerezyme in lumbar spine Z score based on exploratory data and in relation to comparing each patient group with its baseline rather than comparing between groups. To claim that VPRIV significantly improved lumbar spine BMD and Cerezyme did not, based on exploratory data, was misleading and inaccurate. The Appeal Board considered that, on balance, by making claims that were ruled to be misleading and inaccurate, Cerezyme had been disparaged and thus it ruled a breach of the Code. Genzyme's appeal on this point was successful.**

**Genzyme considered that the press release was promotional and failure to certify it was in breach of the Code.**

**The Panel noted that the Code required certain non-promotional material be certified. The material listed did not mention press releases; however, it did include 'material relating to working with patient organisations'. The Panel considered that this clause thus required that material sent proactively by a company to a patient organisation, including, *inter alia*, press releases, should be certified. The Panel considered that the provision of the press release to the patient organisation triggered the certification requirements and ruled breaches of the Code. These rulings were appealed by Shire.**

**The Appeal Board noted its rulings above. The Appeal Board noted that press releases should not promote medicines. However as a consequence of its ruling the press release needed to be certified irrespective of whether it was provided to a patient organisation. The Appeal Board upheld the Panel's rulings of breaches of the Code. Shire's appeal on this point was unsuccessful.**

**Genzyme alleged that as the press release was promotional it needed prescribing information.**

**The Panel noted its ruling above that the press release was not promotional and considered that thus it did not require prescribing information. No breach of the Code was ruled. This ruling was appealed by Genzyme.**

**The Appeal Board noted its ruling above. The Appeal Board considered that the inclusion of prescribing information would not make the item at issue acceptable. Press releases should not promote medicines. However, as consequence of its ruling above, the item was promotional and thus the Appeal Board ruled a breach of the Code. The appeal on this point was successful.**

**Genzyme alleged that Shire's numerous breaches of the Code were so serious as to bring discredit upon, and reduce confidence in, the pharmaceutical industry.**

**The Panel had concerns about the content of the press release. It was not a fair reflection of the study. The Panel noted that Clause 2 was a sign of particular censure and reserved for such use. The Panel considered that when assessing the acceptability or otherwise of claims in a press release companies should be mindful of the intended audience. Companies should be cautious when material was aimed at the consumer press or provided to a patient organisation. The Panel noted its comments and rulings about the press release above. The Panel considered that the implication that exploratory findings were of statistical and clinical significance in a press release directed at, *inter alia*, a patient organisation was wholly unacceptable and brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed by Shire.**

**The Appeal Board considered that Shire should have taken much greater care to ensure that the press release accurately reflected the study and its results. There had not been a new medicine in this disease area for a number of years and understandably there would be much interest from patients and their families. To present exploratory endpoints in such a way as to imply statistical and clinical significance was unacceptable. The Appeal Board noted its rulings of breaches of the Code. The Appeal Board considered the content of the press release and its subsequent proactive provision to a patient organisation was wholly unacceptable and brought discredit upon, and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.**

**Genzyme alleged that Shire had failed to comply with all applicable provisions of the Code.**

**The Panel considered that Shire had failed to comply with all applicable codes as required and a breach was ruled. This ruling was upheld by the Appeal Board on appeal by Shire.**

Genzyme Therapeutics Ltd complained about a VPRIV (velaglucerase alfa) press release issued by Shire Pharmaceuticals Ltd entitled 'Shire's VPRIV (velaglucerase alfa for injection) Shows Significant Improvement in Gaucher-Related Bone Disease'. Genzyme alleged that the press release promoted VPRIV and contained disparaging comparisons with its product Cerezyme (imiglucerase) that were misleading, unbalanced and unsubstantiated.

VPRIV was indicated for long-term enzyme replacement therapy in patients with type 1 Gaucher disease. Cerezyme was indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic (type 1) or chronic neuronopathic (type 3) Gaucher disease who exhibited clinically significant non-neurological manifestations of the disease.

Genzyme noted that the press release was initially on the homepage of Shire's global website under the headline 'Latest News' but was subsequently moved and could currently be accessed under two separate tabs, 'Media' and 'Investors'. Although the company's UK site did not include the press release, Shire's global website was accessible by consumers and health professionals. Shire also provided a copy of the press release through its UK public relations agents to the patient group for Gaucher disease in the UK, The Gauchers Association.

Moreover, Genzyme alleged that as Shire appeared to have provided the press release to several newswires with UK circulation, the company intended it to reach a broad UK audience. One newswire advertised on its website that subscribing companies could 'gain access to thousands of print and broadcast outlets, journalists, bloggers, financial portals, social media networks, website and content syndication channels to target audiences'. The press release was picked up by at least one content provider which had a broad array of mainstream media subscribers. Genzyme noted that the story was covered by numerous UK media outlets, including, but not limited to KeyPharma News, 'Vpriv shows significant improvement in Gaucher-related bone disease' (2 July 2012); Health Daily Digest, 'Shire's Vpriv Beats Sanofi's Cerezyme in Treating Gaucher disease' (29 June 2012); FiercePharma, 'Shire's Gaucher drug beats Cerezyme in bone study' (28 June 2012); SCRIP Intelligence, 'Shire goes toe-to-toe with Genzyme as trial differentiates Gaucher's premium' (28 June 2012); EuroBiotechNews, 'Shire attacks treatment monopoly of Sanofi' (29 June 2012); The Pharma Letter UK, 'Shire's VPRIV shows significant improvement in Gaucher-related bone disease' (28 June 2012); and PharmaTimes Online, 'Shire's VPRIV outshines Genzyme's Cerezyme on bone density' (29 June 2012). Genzyme submitted that the titles of these articles underscored the misleading nature of the press release. Further, two of the individuals identified in the press release as sources of additional information had UK phone numbers.

Genzyme noted that the press release summarized a scientific poster that was presented by one of the authors at the European Working Group on Gaucher Disease (EWGGD) meeting on 28-30 June 2012. However, the press release went beyond the presentation of scientific data in the poster and made comparative/superiority claims that were misleading and based on unsound statistics. These claims were to the detriment of both patients and physicians. Genzyme considered these and the other multiple breaches of the Code detailed below, which resulted in this disparaging promotion to the public, were so egregious as to risk bringing discredit to the industry.

Genzyme stated that in inter-company dialogue the fundamental premise of Shire's response to the allegations was that the press release was not promotional, did not make comparative claims and, therefore, was not required to meet certain provisions of the Code, including the certification requirements in Clause 14.1. Genzyme alleged that both of these assertions were wrong as a matter of the Code, law and fact.

First, the Court of Justice of the European Union (Case C-421/07 'Criminal proceedings against Frede Damgaard') had concluded that any information regarding the properties or availability of a medicine which was intended or likely to influence, either directly or indirectly, the behaviour of patients or the general public constituted promotion. Second, Clause 1.2 of the Code similarly defined 'promotion' as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines'. Third, numerous opinions of the Authority demonstrated that, in the view of the Code of Practice Panel, press releases could be considered promotional. For example, in Case AUTH/2355/9/10, the Panel considered a short description of a press release on a corporate website and the press release itself were advertisements for a medicine aimed at, *inter alia*, the public and in Case AUTH/2201/1/09 the

Panel ruled that a press release raised unfounded hopes of successful treatment and, in effect, encouraged patients to ask for a specific prescription medicine. The Panel concluded that the release was promotional.

Genzyme stated that given the nature of distribution and content of the press release, any attempt to take it outside the application of EU and related implementing UK provisions governing promotional materials by claiming that it was 'a corporate press release .... directed and intended for review by investors' was without merit. This document was indisputably promotional material. The press release was distributed widely in the UK through placement on the homepage of Shire's global website, distribution through its public relations agents to the UK patient group and publication by various UK and European newswires. Moreover, the press release did not simply and objectively describe study data or the related poster but clearly extended well beyond 'legitimate scientific exchange' permitted during drug development. It made broad and unqualified claims about the superiority of VPRIV over Cerezyme and the effectiveness of VPRIV to treat Gaucher-related bone disease that were not included in the underlying poster and were unsubstantiated and misleading. The press release was thus promotional and must, therefore, comply with relevant provisions of the Code. As demonstrated below the press release did not so comply. Moreover, even if the Panel considered that the press release was non-promotional, it still must comply with numerous provisions of the Code discussed below, including requirements relating to information, claims and comparisons in Clause 7 and the balanced and factual presentation of information in Clause 22.2.

Genzyme noted that Shire also stated during inter-company dialogue that the press release made 'no direct comparisons' between VPRIV and Cerezyme. However, Article 2(c) of the EU Directive on misleading and comparative advertising, the provisions of which were reflected in Clause 7.2, defined comparative advertising as 'any advertising which explicitly or by implication identifies a competitor or goods or services offered by a competitor'. Moreover, Clause 7.2 stated that, 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis'.

Genzyme stated that consistent with this position, the Authority had, on numerous occasions, found comparative claims in breach of the Code. For example, in Case AUTH/2147/7/08 the Panel concluded that within the context of a press release a claim that one product had 'unmatched cervical cancer protection' (emphasis added) based on a comparison of efficacy rates in separate Phase III trials was 'misleading, unsubstantiated and exaggerated' in breach of Clauses 7.2, 7.4 and 7.10 of the Code. In Case AUTH/2126/5/08 the Panel considered an allegation that, *inter alia*, a letter to prescribing advisors, a press release and a symposium disparaged bisphosphonates by suggesting that concomitant use of acid suppressants could reduce their effectiveness. The claim was based on three studies all of which concluded that there might be an association and suggested further investigation. The Panel noted that when a clinical or scientific issue existed which had not been resolved in favour of one generally accepted view point, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel concluded that the quality of the data cited could not substantiate the robust unqualified claims that had been made. Further, the Panel determined that the press release at issue was not balanced, did not reflect the data accurately and was thus in breach Clause 7.2.

Genzyme alleged that the press release represented clear and evident breaches of the Code. Genzyme had been unable to resolve these issues with Shire through inter-company dialogue. Given the wholly unjustified and groundless claims in the press release about Cerezyme, Genzyme submitted that the most appropriate corrective action would be for the Panel to require Shire to withdraw the document from its website with immediate effect. In addition, Genzyme requested that Shire be obliged to contact all third parties to whom the press release was distributed, including all journalists who wrote in response to the press release, to inform them that the press release had been withdrawn with detailed scientific and medical reasons as to why.

Shire considered Genzyme's complaint was without foundation. The press release was a non-promotional communication which presented data from a head-to-head, non-inferiority study of genuine interest to investors and the scientific community. Genzyme had not objected to the underlying study or the poster presenting the data at the EWGGD, which was the basis for the press release. Contrary to Genzyme's allegations, the press release did not make any claims of clinical superiority of VPRIV vs Cerezyme; it accurately reported the presentation of findings of an exploratory endpoint of the head-to-head study. In these circumstances, Genzyme had no basis for contesting the content of the press release. Genzyme had also alleged in civil proceedings in the US under the Lanham (Trade marks) Act, that the press release constituted false advertising, in respect of which Shire had filed a Motion to Dismiss. Shire submitted that Genzyme's actions in the UK and US were a regrettable and unwarranted tactic to escalate commercial grievances in order to stifle scientific debate around this new and important data and distract commercial operations.

Shire submitted that Gaucher disease was a rare, inherited, multi-system disease, which occurred when a deficiency of the lysosomal enzyme, glucocerebrosidase (GCB), led to tissue and organ damage. Skeletal complications occurred frequently the treatment of which represented a significant unmet medical need.

Shire stated that the clinical development program

of VPRIV was the largest, most comprehensive clinical development program to date for an enzyme replacement therapy (ERT) for Gaucher disease. The program was initiated in 2004 and regulatory approval and commercialization of VPRIV was originally planned for mid to late 2011. This strategy changed in June 2009 when Genzyme announced it had viral contamination of its manufacturing facility which posed a significant obstacle to the company's ability to provide Cerezyme and other treatments to patients for an indeterminate period of time. Through close partnership with regulatory agencies, as well as expanded access programs, Shire was able to meet the needs of hundreds of type 1 Gaucher patients worldwide who could no longer access Cerezyme. Since late 2009, Shire had provided patients with uninterrupted access to VPRIV at the dose and frequency prescribed by their doctors in all approved markets. These supply issues together with the US approval of another therapy for Gaucher disease had resulted in approximately a 40% decline in global sales of Cerezyme since 2009.

Shire submitted that the data reported in the press release was obtained from Study HGT-GCB-039, a multi-centre, randomised, double-blind, parallel-group, non-inferiority study of Gene-Activated human GCB ERT (velagucerase; VPRIV) compared with imiglucerase in patients with type I Gaucher disease, and its extension study (HGT-GCB-044). Information on the primary and secondary endpoints of Study 039 was published in November 2010. Bone mineral density (BMD) was prospectively defined as an exploratory endpoint of Study 039 and was assessed through DXA (dual-energy x-ray absorptiometry) scans of the lumbar spine and femoral neck.

In summary, Shire stated that the EWGGD poster authored by numerous independent Gaucher experts presented the improvement from baseline in BMD Z-scores at certain pre-specified time-points within each treatment arm (VPRIV and Cerezyme, respectively). Statistical significance was achieved, based on the corresponding 95% confidence intervals, at the 0.05 nominal level of the 9-month mean BMD change from baseline in lumbar spine in the VPRIV group. Given that treatment of the skeletal manifestations of Gaucher disease represented an ongoing clinical concern in the Gaucher disease community, this was newsworthy and important to investors and scientists alike. Patient organisations were an important part of the scientific community for Gaucher disease. Indeed, the EWGGD included patient organisations and, as the European Gaucher Alliance was a 'partner organisation' for the event, representatives from The Gauchers Association attended the 2012 meeting in Paris (28-30 June 2012) and would have seen Shire's poster.

Shire submitted that the press release summarised the BMD results obtained from Study 039 that were presented in greater detail in the poster presented at EWGGD. This was the first presentation of these data. Shire noted that Genzyme had not contested the poster itself, or its underlying findings. The press release did not go beyond the scientific data presented in the poster.
Shire considered that the press release was a non-promotional communication aimed at the investor community (potential and current) and relevant scientific and medical media (which included certain relevant patient organisation media). Whilst the press release was not a price sensitive mandatory announcement, Shire considered the data was newsworthy, important to the corporate and scientific communities and in keeping with what was disclosed by other pharmaceutical companies. The press release was formally reviewed and approved in accordance with Shire's internal procedures.

Shire submitted that, consistent with the poster, the press release did not specifically compare VPRIV and Cerezyme, nor did it make statements of clinical superiority. This was neither the effect, nor the purpose of the press release. Because BMD was pre-specified in the protocol for Study 039 as an exploratory endpoint, no confirmatory conclusions were drawn and no comparisons between treatment arms were made.

In summary, Shire submitted that the non-promotional information presented in the press release was accurate, balanced, fair, objective and unambiguous.

Shire stated that, in these circumstances, Genzyme had no basis for contesting the content of the press release; that it had done so prompted Shire to question Genzyme's motives. Shire considered that the present complaint, together with the civil proceedings brought by Genzyme in the US regarding the same press release, represented a concerted commercial strategy.

In the context of this complaint, Shire disputed Genzyme's claim that it had engaged in inter-company dialogue in 'an earnest attempt at conciliation'. It was regrettable that Genzyme did not take the opportunity to meet with Shire's medical director and was unwilling to await further clarification from Shire's statisticians before complaining to the PMCPA. Genzyme's attitude to inter-company dialogue was reflected in its comment in a telephone conversation, namely that the conciliatory process was 'part of the game'.

Shire refuted Genzyme's allegations in full, including that Shire had brought discredit upon the pharmaceutical industry in breach of Clause 2 of the Code and further that it had 'wilfully' breached the Code through a 'systematic and comprehensive violation of at least six separate clauses of the Code'. These serious allegations potentially damaged Shire's reputation, and were entirely without foundation. As a responsible pharmaceutical company, Shire would never wilfully breach the Code, nor any other applicable law or regulation.

Following a request for further information, Shire submitted that the clinical trials NCT00553631 and NCT635427 on ClinicalTrials.gov were study HGT-GCB-039 and open label extension study HGT-GCB-044, respectively. The data from these studies was the basis for the press release.

Shire provided a schedule setting out the data from these studies that had been made public. As yet there had not been a substantive publication of HGT-GCB-039 in a peer reviewed journal, although this was planned. The extension study HGT-GCB-044 was ongoing. Publications to date had been as posters with abstracts sometimes being included in the scientific journals depending on the nature of the congress. The data from the studies had been published in a phased manner, starting with the primary and secondary endpoints in November 2012 and the first BMD data in June 2012 at EWGGD. Where newsworthy, Shire also issued a press release. Copies of the posters and press releases referred to in the schedule were provided.

**1 Claims and comparisons with Cerezyme**

**COMPLAINT**

Genzyme alleged that comparisons in the press release were not accurate, balanced, fair or based on up-to-date information. They were based on an analysis of exploratory endpoints in a small subgroup using treatment arms that had significant and relevant differences at baseline. Put simply, this analysis was not designed properly to assess changes in bone mineral density (BMD). The press release also selectively focused on some data and endpoints, but not others.

During inter-company dialogue, Shire argued that the press release did not make any direct comparison between Cerezyme and VPRIV and that the information and claims made did not breach Clause 7.2. Genzyme strongly disagreed with this.

Shire had asserted that BMD was pre-specified as exploratory and measurements were performed during the blinded phase of the study, thereby providing for a more robust analysis.

Genzyme noted that the comparison of changes in BMD for patients taking VPRIV and Cerezyme was based on a number of subgroup analyses that were conducted retrospectively on data collected from the original 2008-2009 Phase III study. BMD was not a primary or secondary endpoint of the study; rather, BMD was measured as an 'exploratory' endpoint. While Shire asserted that the analysis of the data was more robust because BMD was pre-specified as exploratory and the study was blinded, Genzyme considered that this did not validate the analyses. As an 'exploratory' endpoint, BMD Z-scores could not properly be used as evidence of clinical superiority. Although the statement that the evaluation of BMD was exploratory was buried in the fifth paragraph of the press release, it did not cure the unbalanced and unfair nature of the press release. Genzyme noted that in Case AUTH/2433/8/11, the Panel stated that, 'the Code required claims in promotional material to be capable of standing alone as regards accuracy etc. In general, claims should not be qualified by the use of footnotes and the like'.

Genzyme considered that as the study at issue was designed to test for endpoints other than BMD, the subject inclusion and exclusion criteria, the number of subjects enrolled, and the criteria to randomize subjects between treatments all were designed to demonstrate changes in these primary and secondary endpoints with sufficient statistical power and significance. The trials were not designed to do the same for changes in BMD, and consequently, they could not support comparative/superiority efficacy claims regarding BMD. Despite this, the press release presented a misleading impression that the statistical significance and comparative/superiority efficacy claims were properly derived from an analysis of a prospectively defined primary endpoint. Shire had asserted that presentation of the median allowed for a fair presentation of the central value, and unlike the mean, was not influenced by outlying factors. The imbalance between the two treatment arms at baseline was addressed by repeating the analysis with a cohort of patients with baseline lumbar spine Z-scores < -1.

Genzyme alleged that the press release selectively used mean and median data to convey the message that patients on VPRIV showed greater improvement in BMD than patients on Cerezyme. Specifically, the press release only included information on the median baseline Z-scores and not the mean or average baseline, even though when describing improvements in BMD, the press release switched to mean changes from baseline. While Shire argued that the median allowed for a fair presentation of the central value and was not influenced by outlying values (unlike presentation of the mean), this argument was not credible when the press release subsequently switched to mean changes from baseline. In addition, the median baseline Z-scores were dramatically closer than the mean baseline Z-scores. As a result, the press release conveyed a misleading message that the patients' BMD levels were more comparable than they actually were.

Genzyme noted that the patients in the VPRIV group had a greater baseline BMD deficiency than patients in the Cerezyme group; thus, the conclusion that patients on VPRIV showed greater improvement in BMD than patients on Cerezyme was not a like-for-like comparison. The mean baseline lumbar spine BMD Z-score for VPRIV patients (when certain patients were appropriately excluded) was -1.56, and the mean baseline lumbar spine BMD Z-score for the Cerezyme cohort was -0.47. In fact, 4 of the 8 (50%) Cerezyme patients had normal bone density, compared with only 2 of the 11 (18%) VPRIV patients. This was an important and meaningful imbalance between the two groups with regard to the proportion of patients with 'normal' BMD. Patients who began with normal BMD generally would not increase BMD levels at a significant rate above normal. Thus, VPRIV patients on average had significantly more room for improvement in BMD levels. Accordingly, the conclusion in the press release, that patients on VPRIV showed more improvement in BMD compared with patients on Cerezyme, was based on patients who started from different baselines, who had different capacities to improve and who might improve at different rates as a result. In fact, had Shire adjusted properly for baseline differences, patients taking Cerezyme might have demonstrated a greater percentage improvement in BMD than patients taking VPRIV. As

such, the press release made inaccurate and misleading superiority claims.

Genzyme noted that although Shire acknowledged the imbalances with baseline lumbar spine Z-scores, it asserted that the results were robust because it had obtained similar results after adjusting for this difference. However, the results after adjusting for this difference were from a 'within-group' analysis, which could not support comparative/superiority efficacy claims. Thus, it was misleading for Shire to fail to disclose in the press release that no conclusion regarding group-to-group comparisons could be made based on the data from the study.

Genzyme further noted that Shire had asserted that the sample size of 19 patients was sufficiently powered. The number of patients available to participate in clinical trials in rare diseases was less than in trials in more common conditions.

Genzyme stated that to determine whether a clinical study was sufficiently powered, it was not enough to simply look at the number of patients involved. For a clinical study to be sufficiently powered, it needed to be prospectively designed to determine the number of patients that was required to detect a particular treatment effect. As such, a properly designed clinical study might be sufficiently powered to claim statistical significance based on a small sample size, but an improperly designed clinical study might not be able to claim statistical significance despite a large sample size. The Panel recognized this principle in Case AUTH/2377/12/10, noting that a study '…was not powered to detect a difference in such a small group [subgroup with the highest baseline HbA1c]' and finding that 'the results from the high baseline HbA1c had been over emphasized and in that regard the presentation of the data in the e-detail was misleading….'.

Genzyme alleged that Shire's BMD analysis was based on a subgroup of a subgroup, and was not prospectively designed to be sufficiently powered for a sample size of 19 patients. Further, because the BMD analysis was exploratory, the studies were not designed to be sufficiently powered for this analysis. Consequently, this retrospective BMD analysis was insufficiently powered to draw statistically significant conclusions. In spite of these methodological flaws, the press release presented comparative/superiority claims of efficacy based on this flawed analysis.

Shire had denied the allegation that the subgroup endpoint of lumbar spine BMD had been cherry picked. It was common for a press release to only present data showing statistical significance, and the press release additionally reported that femoral neck changes were insignificant at 9 or 24 months.

Genzyme noted that the title of the press release made the general conclusion that VPRIV showed significant improvement in 'Gaucher-Related Bone Disease'. However, the body of the press release only reported the data relating to BMD measurements in the lumbar spine. For example, Shire did not include femoral neck BMD Z-scores because VPRIV was not shown to have a positive effect on femoral BMD after 9 months. Thus, the BMD Z-scores were presented selectively and presented an inaccurate and misleading efficacy claim that VPRIV improved BMD more than Cerezyme.

In addition, while Shire's Study 39 was a well-designed, randomised controlled trial, the analysis of BMD data was a retrospective, subgroup analysis of exploratory endpoints. The press release relied on this analysis to make comparative/superiority efficacy claims.

Shire had asserted that the press release summarized scientific data from an abstract that was presented at the EWGGD meeting, and this was the most up-to-date evidence on BMD data relating to enzyme replacement therapy in Gaucher disease.

Genzyme however alleged that the press release did not merely summarize the scientific data from the abstract presented at the EWGGD meeting. It went beyond reporting the scientific data and made comparative/superiority claims. In addition, the BMD data presented in the press release did not constitute an up-to-date evaluation of all the evidence because it did not include data that showed that Cerezyme had statistically significant results on bone disease, including BMD measurements.

Genzyme alleged that the analysis in the press release was not accurate, balanced, fair, objective, unambiguous, or based on an up-to-date evaluation of all the evidence in breach of Clause 7.2.

**RESPONSE**

Shire submitted that Genzyme's allegations were based on the premise that Shire had compared VPRIV and Cerezyme and claimed clinical superiority of its own product over Genzyme's. However, Genzyme's assumption was without foundation. The press release fairly summarised the results from clinical trial research that were first presented at the EWGGD, without concluding that VPRIV was more effective than Cerezyme. The press release accurately stated the improvement in BMD in a particular clinical study comprised two treatment arms, each with its own baseline. Because BMD was pre-specified in the protocol for Study 039 as an exploratory endpoint, no confirmatory conclusions were drawn and no comparisons between treatment arms were made. Shire separately assessed within-patient change from baseline within each treatment group at nine and 24 months. A clinically and statistically significant improvement in BMD compared with baseline after nine months of treatment with VPRIV was shown. Cerezyme patients did not show a statistically significant improvement in BMD from baseline at nine months. However as no comparisons were drawn, no claims of clinical superiority were made.

Shire stated that the press release clearly stated that BMD was evaluated as an exploratory endpoint; it was in the same sentence as the information regarding improvement from baseline in mean lumbar spine Z-scores in each of the two treatment groups (paragraph 5 of the press release). These were factual statements, objectively reported, from

the comprehensive data that were prospectively collected and included in detail in the EWGGD poster (which, as already noted, Genzyme had not objected to). More specifically, as regards statistical significance, 95% confidence intervals for the within-group mean change from baseline was important information and as such was reported in the press release. As regards clinical significance, BMD was a globally recognised surrogate marker for bone disease characterised by a loss of calcium. Bones might be categorised by the WHO criteria as normal, osteopenic or osteoporotic depending on the BMD score as measured by DXA scans (dual-energy x-ray absorptiometry). Improvements in BMD could therefore be translated into clinical improvement if the patient moved from one category to a higher one eg from osteoporosis to osteopenia.

Shire submitted that DXA scans were the gold standard for assessing BMD. To ensure that its presentation of the 2 year results reflected the most robust data, Shire undertook a rigorous and lengthy analysis so as to confirm and validate its original findings. The initial BMD data and statistical summary of the results were presented during a confidential investigator meeting in the spring of 2011. On the basis of this presentation, the investigators recommended that the DXA machines at the various sites be re-calibrated and standardized to assure that the findings were not subject to differences and drift of the radiographic machines used in this multi-centre study. Re-calibration and standardization of the data was initiated in the summer of 2011 and completed in the spring of 2012. Re-analysis of the standardized data was consistent with the earlier findings and the results were subsequently presented for the first time to the scientific community for Gaucher disease at the EWGGD meeting in Paris (28-30 June 2012) in the form of the poster.

Further, the data reported in the press release was consistent with previous data/literature. The nine-month mean change from baseline observed with VPRIV was consistent with the lumbar spine BMD improvements seen in the published Phase I/II clinical trial TKT025EXT (Elstein *et al* 2011) and the other naïve Phase III clinical trial (TKT032). The nine-month mean change from baseline (+0.06 without concomitant bisphosphonates; 0.10 including patients on concomitant bisphosphonates) observed with Cerezyme was consistent with the lumbar spine BMD improvements reported in the literature (+0.13/year; 0.09 at nine months, as reported in Wenstrup *et al* 2007 – a Genzyme sponsored publication).

The target audience of the press release (the investor community and relevant scientific and medical media) would readily understand the significance of the findings reported in the press release, and further that no claims of clinical superiority were made, implied or intended. The BMD endpoint was specifically stated to be 'exploratory', and the entire thrust of the press release highlighted the statistically significant improvement in patients treated with VPRIV (with the results in patients treated with Cerezyme reported as an ancillary finding). This was evident from the title of the press release: 'Shire's VPRIV (velaglucerase alfa for injection) Shows Significant Improvement in Gaucher-Related Bone Disease'. The first two paragraphs further explained that the data demonstrate that VPRIV improved Gaucher-related bone disease (without any reference to Cerezyme). Cerezyme was mentioned in the sub-heading to the press release, as well as paragraphs 4 and 5, by way of explaining that the data came out of a head-to-head trial. Shire was nevertheless fully transparent about the fact that the trial did not measure BMD head-to-head; from the wording it was therefore apparent that the two treatment arms were measured separately, and that what was measured was the degree of improvement from baseline in each cohort.

Shire did not dispute that information, even in a non-promotional context, must comply with Clause 7; it maintained that the press release did comply with that clause. Shire submitted that the broad definition of comparative advertising in the EU Directive on misleading and comparative advertising, referred to by Genzyme, was not relevant because the press release was not promotional. Reporting on data generated from two treatment arms did not mean that the underlying message of the press release was to compare the two products. Shire could not have fairly or accurately reported the results of its research on VPRIV and Cerezyme without identifying the products at issue. If Shire had ignored the data generated from Cerezyme patients and issued a press release which suggested that the study was only of VPRIV, that in and of itself would have been inaccurate and misleading and given Genzyme grounds for complaint.

Shire considered that, in the circumstances, Genzyme's comment that the PMCPA had on numerous occasions found comparative claims between medicines to be in breach of the Code was totally irrelevant. Genzyme referred to Case AUTH/2147/7/08 where the Panel ruled that, within the context of a press release, the claim that one product provided 'unmatched cervical cancer protection' misleadingly implied that the product had been unequivocally proven to be clinically superior to its competitor with regard to cervical cancer protection (when in fact there was no head-to-head data). In contrast, however, the press release at issue made no comparative/superiority claims whatsoever (l*et al*one such a broad claim as was at issue in Case AUTH/2147/7/08). Further, in that case, the claim was made on the basis of a comparison of efficacy rates in separate Phase III trials. In contrast, in the present case, improvements in the two treatment arms of the same trial were respectively compared to baseline. Genzyme also referred to Case AUTH/2126/5/08, which concerned claims based on three studies indicating that there might be an association between the concomitant use of acid suppressants and a reduction in the effectiveness of bisphosphonates. In that case, the Panel noted that when 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. It concluded that

the quality of the data cited could not substantiate the strong unqualified claims made. Again, that case was not relevant here: no promotional claims were made and it was manifestly clear that the data reported related to an exploratory endpoint.

As explained above, the press release did not contain any statements or claims of clinical superiority. This clarification was fundamental to Shire's response to allegations in Points 1, 2 and 3 and it was in this context that Shire addressed the detail of Genzyme's allegations, below.

- Subgroup analyses and exploratory endpoint

Shire submitted that Genzyme attempted to undermine the data reported in the press release on the basis that changes in BMD were 'based upon a number of subgroup analyses'. However, it was important to clarify the points set out below.

- It appeared that Genzyme might be objecting to the fact that the adult population represented a subgroup of the intent-to-treat population. As per the study protocol, BMD assessments were not evaluated in children. In other words, whilst the adult population was a subset of the intent-to-treat population, this was the group of patients for whom DXA was performed according to the study design (total adult population n=24). Therefore, the adult population did not represent a subgroup in the conventional use of the term.
- Shire performed a subgroup analysis of those adult patients who did not receive concomitant bisphosphonates (n=19). This was done in order to evaluate the bone related efficacy of enzyme replacement therapy (ERT) without concomitant medication that might influence bone improvement.
- Bisphosphonates were known to improve BMD in the general population and similarly had been shown to improve BMD in patients with Gaucher disease.
- In order to evaluate the effect of VPRIV on lumbar spine and femoral neck BMD without any additional effects of bisphosphonates, all analyses were repeated in the subgroup of patients who had not used bisphosphonates.
- Accordingly, this was an important subgroup to analyse as it provided an unadulterated estimate of the effect of enzyme replacement therapy (ERT) on BMD.
- Indeed, in the analysis published in 2007 from Genzyme's ICGG Registry, Wenstrup *et al* also included patients on ERT treatment alone.
- The treatment effect was directionally the same and similar in magnitude between the adult population (as a whole) and the subgroup of that adult population who did not use bisphosphonates, indicating that the improvement in BMD following treatment was not the result of concomitant bisphosphonates.
- The press release appropriately and clearly stated that the results obtained within the entire adult population were similar to the results obtained within the subgroup of adults who did not receive concomitant bisphosphonates.

Shire further submitted that, whilst Genzyme commented that the analyses 'were conducted retrospectively on data collected from the original 2008-2009 Phase III study', it was important to clarify that the data were prospectively collected at pre-defined time points, as per the study protocol.

Genzyme also objected to the fact that BMD was measured as an exploratory endpoint and, as such, could not be used as evidence of clinical superiority. As previously noted, neither statements nor claims of comparison or superiority were made in the poster presentation from the EWGGD meeting, or in the press release at issue. Because BMD was pre-specified in the Study 039 protocol (included in the initial design) as an exploratory endpoint, no confirmatory conclusions were drawn, nor were any comparison made between arms. Nevertheless, statistical significance or lack of statistical significance of the mean change from baseline to nine months within each treatment group was newsworthy information, and as such was stated in the press release.

Shire disputed Genzyme's claim that the statement regarding the exploratory endpoint was 'buried' within the text, thus making the press release unbalanced and unfair. In fact, information describing the specific endpoint analyzed and reported on at the 2012 EWGGD meeting was outlined within the main body of the press release. It was clearly and prominently placed within the section which summarized many of the results reviewed in the poster presentation including:

- Median lumbar spine Z-scores at baseline for VPRIV;
- Median lumbar spine Z-scores at baseline for Cerezyme;
- Mean change from baseline in lumbar spine Z-scores for VPRIV;
- Mean change from baseline in lumbar spine Z-scores for Cerezyme;
- Mean change in lumbar spine Z-scores following switch from Cerezyme to VPRIV at nine months;
- Mean change from baseline in femoral neck Z-scores at nine and 24 months for both groups; and
- Mean changes from baseline in BMD (lumbar spine and femoral neck) within the groups after excluding data from 5 patients on concomitant bisphosphonates.

Shire submitted that, accordingly, the statement was included at the appropriate point in the text. Genzyme's reference to Case AUTH/2433/8/11, where the Panel stated that 'claims should not be qualified by the use of footnotes and the like' was irrelevant because the press release did not make promotional claims and the statement that the endpoint was 'exploratory' was not placed in a footnote, but clearly beside the results (as was appropriate for the target audience).

Finally, Genzyme claimed that the press release presented a misleading impression that the statistical significance and comparative/superiority efficacy claims were properly derived from an

analysis of the prospectively defined primary endpoint. Shire refuted this allegation. No 'between group' comparison was made in the EWGGD data analysis and subsequent poster presentation (the basis for the press release), nor in the press release itself. Based on the within-group statistical analysis, and as stated in the press release, statistical significance was achieved, based on the corresponding 95% confidence intervals, at the 0.05 nominal level of the nine-month mean BMD change from baseline in lumbar spine within the patients receiving VPRIV. Based on the separate within-group statistical analysis, patients within the Cerezyme cohort did not show a statistically significant improvement in BMD from baseline at nine months.

- Use of mean/median data and differences in treatment groups

Genzyme claimed that the press release selectively used mean and median data in order to convey the message that patients on VPRIV showed greater improvement in BMD than patients on Cerezyme. Genzyme appeared to recognise in this allegation the separate within-group analysis, which was not consistent with its position on comparisons that was expressed in Genzyme's other allegations.

Shire noted, however, that it was important to clarify that the presentation of the median baseline lumbar spine Z-scores within each group allowed for a fair presentation of the central value (50% above; 50% below) and was not influenced by outlying values as in the case with the mean. Whilst both median and mean baseline scores were presented in the poster, the decision to use the median baseline Z-scores in the press release took into account the fact that these scores were different between the two groups and, further, the fact that the distribution of baseline Z-scores did not follow a normal distribution curve. The EWGGD poster presentation, the basis of the press release, acknowledged these baseline imbalances. As a result, to identify a homogeneous cohort of patients who had lower BMD scores at baseline, the within-group analysis was repeated in patients with a baseline lumbar spine Z-score < -1. Shire noted that, in that case, the results were consistent with the initial analysis.

In contrast, the within-patient changes from baseline to nine months were normally distributed (bell shaped; mean ~ median). As a result, the mean change from baseline to nine months and the corresponding 95% confidence intervals were presented.

Accordingly, Shire had not selectively used mean and median data selectively in order to convey the message that VPRIV patients showed greater improvement in BMD than patients on Cerezyme. No comparative/superiority claims were made, implied or intended; mean and median data were used appropriately based on the distribution curve.

Shire noted that Genzyme further stated that the greater improvement in patients treated with VPRIV was not a fair comparison because the patients in the VPRIV group had a greater BMD deficiency than those in the Cerezyme group. However, Genzyme's conclusion was not consistent with the results of the study at 24 months. As was mentioned in the study and the press release, improvement in this group who switched from Cerezyme to VPRIV at nine months continued to demonstrate improvement in Z-scores to 24 months. Genzyme's conclusion that 'patients that begin with normal BMD generally will not increase BMD levels at a significant rate above normal' appeared to be inconsistent with its own data published by Wenstrup *et al*.

In response to Genzyme's point that Shire misled in failing to disclose that group-to-group comparisons could not be made, this was not necessary as no comparisons were made or intended.

- Patient sample size

Genzyme claimed that Study 039 was not designed to be sufficiently powered for the BMD analysis because it was based on a subgroup and the endpoint was exploratory. However, Genzyme did not distinguish between comparative and non-comparative exploratory analysis.

It was important to reiterate that no statistical comparison was made in the press release between treatment groups. Shire contended that the study was sufficiently powered for the purposes of the within-group statistical analysis, ie to show the change from baseline for patients receiving VPRIV was significant. Likewise, for the within-group statistical analysis of the Cerezyme group.

Shire reiterated that it was legitimate for the BMD assessment to be based on the adult population and for a subgroup analysis to be taken of patients who did not receive concomitant bisphosphonates.

Shire did not consider Case AUTH/2377/12/10, cited by Genzyme, was relevant. Integral to the Appeal Board's ruling was the presentation of the data on the e-detail page. As regards the Appeal Board's conclusion that the study was not powered to detect a difference in such a small group, this was very fact specific and must be considered within its proper context of the disease area; type 2 diabetes was significantly more prevalent than Gaucher disease (an ultra orphan condition, with an estimated 277 patients currently receiving ERT in the UK).

Further, Shire was puzzled by Genzyme's allegation considering that, on 18 February 2011, Genzyme posted a press release entitled 'Three-Year Data from Phase 2 Trial of Genzyme Gaucher Disease Oral Compound Suggest Sustained or Further Improvement Across All Endpoints', which claimed statistical significance on BMD data extrapolated from a small sample (15 people) (copy provided).

- Selection of data

Shire submitted that bone disease was a significant factor in the lives of Gaucher patients. Eight out of 10 patients had bone involvement that, untreated, might lead to growth retardation in children; acute episodes or chronic bone pain; osteolytic lesions and generalised osteopenia/osteoporosis that led to recurrent fracture and other defects. Some of the

bone disease was ameliorated by ERT. However, it was accepted that response to ERT was slower in respect of BMD than for the haematological parameters, and a significant number of patients still had low BMD and suffered significant bone symptoms despite long-term ERT. Bone disease was therefore a significant unmet need for Gaucher patients and data in this area, especially from controlled studies, would be considered newsworthy. Shire noted that the measurement of BMD in the lumbar spine was the internationally agreed preferred site for measurement.

Shire noted that Genzyme criticised the press release for selectively reporting the lumbar spine BMD data whilst excluding BMD Z-scores relating to the neck of femur. The press release detailed the high-level bone results obtained from Study 039 that were presented in greater detail at EWGGD. As stated in the press release, 'Femoral neck changes from baseline in both cohorts were non-significant (P>0.05) at either nine or 24 months'. In order to be newsworthy, it was common practice in the industry for press releases to present data in detail that achieved statistical significance (the hallmark of evidence based medicine), while still mentioning all other data as was the case here.

Accordingly, the BMD Z-scores were not presented selectively, and the press release was not inaccurate or misleading in the way that the data were reported.

- Reflection of the scientific data and evaluation of the evidence

Genzyme alleged that the press release went beyond reporting the scientific data and made comparative/superiority claims. It further alleged that the BMD data presented in the press release did not constitute an up-to-date evaluation of all the evidence because the press release did not address the existence of data that affirmatively showed that Cerezyme had statistically significant results on bone disease, including BMD measurements.

Shire reiterated that no comparative or superiority claims were made.

The press release was an objective summary of the results presented at the 2012 meeting of the EWGGD. As explained above, the nine-month mean change from baseline observed with VPRIV was consistent with the lumbar spine BMD improvements seen in Shire's published Phase I/II clinical trial TKT025EXT (Elstein *et al*) and the other naïve Phase III clinical trial (TKT032). Further, the nine-month mean change from baseline (+0.06 without concomitant bisphosphonates; 0.10 including patients on concomitant bisphosphonates) observed with Cerezyme was consistent with the lumbar spine BMD improvements reported in the literature (+0.13/year; 0.09 at nine months; (Wenstrup *et al*)).

The press release summarised the most recently published data analyzing the effects of ERT on BMD in Gaucher disease as this was the first time the data were publicly presented from Study 039. As per the protocol, adults underwent DXA scans at baseline and nine months and data were prospectively collected at the pre-defined time points. The primary and secondary endpoints from Study 039 were previously presented (and summarized in press releases) on 1 September 2009 and 4 November 2010. In accordance with Shire's guidance and review process, explained in detail above, Shire disseminated information by way of a press release only when it was genuinely newsworthy, as was the case here.

In summary, the information in the press release was balanced, fair and based on an up-to-date evaluation of all the evidence, in compliance with Clause 7.2 of the Code.

Following a request for further information, Shire submitted that the press release at issue expressly stated that the BMD was evaluated as an exploratory endpoint. As BMD was pre-specified in the protocol for Study 039 as an exploratory endpoint, no confirmatory conclusions were drawn and no comparisons between treatment arms were made or were intended to be made in the press release.

Shire stated that the assessment of BMD and the corresponding statistical analysis were pre-specified in the HGT-GCB-039 and HGT-GCB-044 protocols as exploratory rather than hypothesis driven analyses or confirmatory analyses. Whilst exploratory examinations produce conclusions that might be distinguished from confirmatory or hypothesis-testing analyses, they were relevant and informative. Exploratory analyses could suggest interesting phenomenon or serve as a basis for explaining or supporting findings, so sometimes exploratory analyses were referred to as hypothesis-generating analyses. To ensure that readers were not misled and to facilitate the interpretation of Shire's results, the analyses were clearly described as exploratory in both the poster and press release.

**PANEL RULING**

The Panel noted that it first had to consider whether the press release came within the scope of the Code. The Panel noted that the press release had been issued by Shire plc, in Switzerland. Shire did not provide the requested details about the UK company's role in relation to the press release but noted that it was published on the global, but not the UK, website. There was no reference to the use or availability of VPRIV in the UK although UK contact telephone numbers were provided. Readers were advised to consult local prescribing information and told where to find the US prescribing information. The Panel noted Shire's submission that the press release was not directed to a specifically UK audience. However, the Panel further noted that the press release had been sent to, *inter alia*, The Gauchers Association, a UK patient organisation and therefore considered that the content of the press release came within the scope of the Code and had to comply with it.

The Panel noted that the title of the press release at issue was 'Shire's VPRIV (velaglucerase alfa injection) Shows Significant Improvement in Gaucher-Related

Bone Disease'. Below this, in slightly smaller text, was the prominent subheading 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density'. The press release then detailed the results of a head-to-head Phase III clinical study (HGT-GCB-039) and follow on extension trial (HGT-GCB-044) with VPRIV in relation to lumbar spine BMD, stating, *inter alia*, that clinically and statistically significant improvement from baseline in mean lumbar spine Z-score was seen at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme. The Panel disagreed with Shire's repeated assertions that no comparative or superiority claims were made.

The Panel noted from the entry on ClinicalTrials.gov for the trial HGT-GCB-039 (ClinicalTrails.gov reference NCT00553631) that the title of the study was 'Study of Gene-Activated Human Glucocerebrosidase (GA-GCB) ERT Compared With Imiglucerase in Type I Gaucher Disease'. Under the section 'Purpose' was the statement 'The purpose of this non-inferiority study is to evaluate the efficacy and safety of GA-GCB (velaglucerase alfa) administered every other week in comparison to imiglucerase in treatment naïve patients with type 1 Gaucher disease'. The primary outcome measures were mean change from baseline to month 9 in haemoglobin concentration for each treatment group and the secondary outcome measures as change from baseline to month 9 in platelet counts; change from baseline to month 9 in normalized liver volume; change from baseline to month 9 in normalized spleen volume; change from baseline to month 9 in plasma chitotriosidase; change from baseline to month 9 in plasma chemokine (C-C motif) ligand 18; number of patients who developed antibodies to treatment and a comparison of GA-GCB and imiglucerase on the earliest time to respond as assessed via haemoglobin concentration.

The entry on ClinicalTrials.gov for the trial HGT-GCB-044 (ClinicalTrials.gov reference NCT0635427) noted that the title of the study was 'An Open-Label Extension Study of GA-GCB ERT in Patients With Type 1 Gaucher Disease'. The purpose of the study was to evaluate the long-term safety of every other week dosing of VPRIV intravenously in patients with type 1 Gaucher disease, the primary outcome measure was the evaluation of safety and the secondary outcome measures were the evaluation of haematological parameters and organomegaly.

The Panel noted that the poster (Zimran *et al* 2012), upon which the press release was based, was entitled 'Bone mineral density response to enzyme replacement therapy over 2 years in adults with type 1 Gaucher disease'. It explained that the study HGT-GCB-039 was a Phase III, randomized, parallel-group trial in patients with type 1 Gaucher disease; one group was allocated VPRIV (n=13) and the other Cerezyme (n=11) therapy for 9 months. In the extension study (HGT-GCB-044), which was ongoing, those patients taking VPRIV continued to do so and those taking Cerezyme were switched to VPRIV. BMD was measured for the lumbar spine and femoral neck at baseline, 9 and 24 months relative to baseline. The statistical analysis section of the poster referred to the BMD assessment being pre-specified as exploratory and thus there were no pre-specified hypotheses. The poster went on to state that because there were no specific bone-related inclusion or exclusion criteria in the protocols for the studies and the randomization was not stratified by BMD, there were imbalances between the two treatment arms at baseline such that the mean lumbar spine BMD Z-score in the VPRIV group was -1.56 and -0.57 in the Cerezyme group (although the press release referred to the more closely matched median baseline figures of -1.46 and -0.86, respectively). Additional analyses adjusting for baseline lumbar spine bone status were performed in patients with a baseline lumbar spine T-score <-1 (excluding patients with normal density) and in patients with a baseline lumbar spine Z-score <-1 but this reduced the number of patients in each treatment arm (VPRIV (n=9) and Cerezyme (n=4)). Although this additional analysis confirmed the lumbar spine BMD Z-score results in the wider patient group the Panel noted that there were only 4 patients in the Cerezyme group and more than double that in the VPRIV group.

The Panel noted that despite the limitations of the data noted above, the title and subheading of the press release as set out above was unequivocal. A further statement read 'Results from a head-to-head Phase III study (HGT-GCB-039) of VPRIV and Cerezyme, and follow-on extension trial (HGT-GCB-044) of VPRIV, demonstrate a statistically significant improvement in lumbar spine (LS) BMD in Gaucher patients starting at nine months of treatment with VPRIV ($P<0.05$)'. The only reference to BMD being evaluated as an exploratory endpoint was in a sentence in the fifth paragraph of the press release which detailed how BMD was measured. The Panel noted Shire's submission that exploratory examinations produced conclusions that might be distinguished from confirmatory or hypothesis-testing analyses and could suggest interesting phenomenon or serve as a basis for explaining or supporting findings.

The Panel did not accept Shire's submission that the press release made no comparative claims. The Panel was concerned that the press release was not clear that the extension study from which the BMD results were obtained was not a head-to-head study of VPRIV and Cerezyme; it gave a contrary impression in this regard. The extension study compared BMD results within each group to baseline. The press release was misleading on this point and a breach of Clause 7.2 was ruled. This ruling was appealed by Shire. In addition, the Panel did not consider that it was sufficiently clear from the press release that BMD was a pre-specified exploratory endpoint. The only reference to this was towards the end of the press release and there was no explanation that no confirmatory clinical conclusions could be drawn from such an endpoint. In the opinion of the Panel the press release invited the reader to draw such conclusions. Exploratory endpoints could not be used as the basis for a robust comparison of medicines. The Panel considered that

the press release was misleading in that regard and ruled a breach of Clause 7.2. This ruling was appealed by Shire.

The Panel considered that the allegations about sample size and use of mean/median in relation to the changes in BMD were covered by its comments about the presentation of the BMD data in the press release. The Panel considered that overall the press release was not a fair reflection of the data. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the findings. A breach of Clause 7.2 was ruled. This ruling was appealed by Shire.

The Panel noted Genzyme's allegation that the press release did not include the BMD Z-scores relating to the neck of the femoral bone. The press release stated that the femoral neck changes from baseline in both cohorts were not significant at either 9 or 24 months. The Panel noted its comments and ruling above in relation to BMD. However, and on balance, in relation to the very narrow ground alleged, the Panel did not consider that the press release was misleading solely because it failed to quantify the femoral neck BMD as alleged and thus no breach of Clause 7.2 was ruled. This ruling was not appealed.

**APPEAL BY SHIRE**

- General comments

Shire submitted that the communication and the circumstances of the press release's distribution were explained in its response to the complaint. Shire noted that the intended audience of the press release was the investor community (potential and current), as well as relevant scientific and medical media. This included the media arm of the Gauchers Association, a patient organisation which had an integral role in the scientific community for Gaucher disease.

Shire noted that the Panel concluded that the press release was non-promotional. It therefore ruled no breach of Clauses 22.1 and 4.1 and it characterised the press release as one of the Clause 14.3 categories of non-promotional material. It was in this context that the Panel's rulings of breaches of the Code must now be considered.

Shire stated that it considered the Panel's rulings of breaches were without foundation. In particular, it appeared that the Panel had made certain assumptions without weighing up all the arguments before it. The Panel's ruling did not represent a fair summary of the two sides of this complaint. Specifically, the summary of arguments preceding each ruling was clearly weighted in favour of Genzyme, with no obvious consideration of Shire's position on certain aspects of the case. It appeared that the Panel had either failed to fully consider or not taken into account Shire's detailed arguments. This lack of detailed reasoning in the Panel's ruling, specific examples of which were highlighted in the appeal where appropriate, resulted in an unfair situation for Shire. Indeed, Shire could not fully defend the basis for the press release if the Panel did not fully explain how it reached a particular conclusion.

Shire submitted that this apparent arbitrariness in the Panel's conclusions was particularly obvious in its rulings of breaches of Clauses 7.2 and 7.3. Here, the Panel appeared to have overlooked the clear wording of the press release and concluded that Shire had misleadingly implied that the studies produced (in the Panel's words) 'robust confirmatory comparative data' that VPRIV significantly improved lumbar spine BMD and that Cerezyme did not. It appeared that the Panel had not seriously considered Shire's defence arguments, and had dismissed Shire's position as 'disingenuous', implying that Shire had no legitimate basis to defend against Genzyme's allegations. Shire strongly disputed Genzyme's allegations under Clause 7 and the Panel's ruling in that respect. Even though it was within the Panel's discretion to conclude that the press release breached Clause 7, Shire submitted that it was inappropriate for the Panel to condemn Shire for merely defending itself against Genzyme's complaint when the provisions of the Code were open to interpretation in light of the particular facts at stake. Shire respectfully requested that the Appeal Board considered whether the Panel's use of such pejorative language was appropriate.

Further, Shire considered that in ruling breaches of Clauses 2, and 22.2, the Panel had taken an approach which was inconsistent with previous rulings, as explained in detail below (Points 4 and 8). This represented a violation of the principles of legal certainty and equality. Even if the Appeal Board disagreed with Shire's submissions in all other respects, a ruling that it had brought discredit upon the industry was clearly unwarranted. In this respect Shire reiterated that the press release was non-promotional and it was appropriately disseminated to a knowledgeable audience who would understand what weight should be attached to the data. Further, the dissemination of relevant and newsworthy scientific data through a press release was common practice within the industry. Therefore, a decision that sought to limit the manner in which scientific data could be shared in this fashion must be weighed with great care to avoid stifling the exchange of meaningful scientific and clinical data within the relevant scientific and shareholder communities. Shire further noted that there was uncertainty on the issue of communications with patient organisations as a consequence of their hybrid status in both the patient and scientific communities and the range of experience of such organisations. Accordingly this last factor was of relevance in considering the appropriateness of a ruling of a breach of Clause 2.

- Points 1 and 2

Shire noted that three rulings of breaches of Clause 7.2 were made at Point 1(referred to below as Rulings 1a, 1b and 1c). The Panel considered that the issues at stake in Points 1 and 2 were inextricably linked and Shire had addressed them together due to the subject matter.

Shire submitted that the Panel's ruling of various breaches of Clause 7.2 and one breach of Clause 7.3 (Point 3) stemmed from its conclusion that the press release made improper comparative claims between VPRIV and Cerezyme. Shire firmly denied that any comparison was made or was intended to be made for the reasons explained in detail in its response. In this context, the specific comments and conclusions of the Panel were addressed and refuted below in order to avoid unnecessary repetition.

Shire refuted the Panel's conclusion that it was not clear that the extension study from which the BMD results were obtained was not a head-to-head study of VPRIV and Cerezyme, and that the press release was consequently misleading in breach of Clause 7.2.

First of all, Shire submitted that the Panel incorrectly implied that the BMD results were obtained solely from the extension study (which was not a head-to-head study). In fact, however, the data were obtained from both the VPRIV/Cerezyme head-to-head study (HGT-GCB-039) and the non head-to-head extension study (HGT-GCB-044), in which all patients from the Cerezyme cohort were switched to receive VPRIV. (For the sake of clarity, Shire noted in its response to the complaint it referred to the 039 study and its extension (044) together as defined term 'the 039 Study'). The newsworthy finding of a statistically significant improvement in BMD at 9 months in patients treated with VPRIV came from the original study, which was referred to in the press release as a head-to-head study because this was quite simply a fact. It was therefore included in the press release for the sake of accuracy and completeness.

However, the fact that the original study was correctly identified in the press release as a head-to-head study did not create a misleading impression that the extension study was also a head-to-head study. Rather, the two studies were clearly distinguished by the following wording:

> 'Results from a head-to-head Phase III study (HGT-GCB-039) of VPRIV and Cerezyme, and follow-on extension trial (HGT-GCB-044) of VPRIV, demonstrate a statistically significant improvement in lumbar spine (LS) BMD in Gaucher patients starting at nine months of treatment with VPRIV (P<0.05). Patients participating in the study were administered 60 U/kg every other week of either VPRIV or Cerezyme for nine months as part of the HGT-GCB-039 study. All patients, including those who received Cerezyme, subsequently received 60 U/kg every other week of VPRIV for an additional 15 months in the extension trial (HGT-GCB-044).' (Emphasis added)

It was therefore clear that patients in the original study were treated with VPRIV or Cerezyme, whereas all patients in the extension study were treated with VPRIV. This wording accurately reflected the facts. Further, the wording highlighted in bold above made the distinction between the two studies entirely clear and unambiguous. Indeed, the last sentence reiterated that all patients including those who had received Cerezyme (ie in the original study) subsequently received VPRIV in the extension study.

Moreover, it was not stated or implied that BMD was assessed on a head-to-head basis. As the Panel correctly commented, BMD was compared to baseline within each treatment arm. Notwithstanding that the original study was accurately identified in the press release as a head-to-head study. It was abundantly clear that the only comparisons recorded were changes in Z scores within each treatment arm, measured from baseline. In explaining the data, the word 'baseline' was used four times in the one page press release, which was consistent with the statement at the outset that the data demonstrated that 'VPRIV improves Gaucher-related bone disease by a sustained increase in bone mineral density (BMD)' (emphasis added). The emphasis on improvement in Z scores from baseline was illustrated by the following wording:

- 'Clinically and statistically significant improvement from baseline in mean LS Z-score was seen at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme'. (Emphasis added)
- 'Median LS Z-scores at baseline were [...] in patients treated with VPRIV, and [...] in patients treated with Cerezyme'. (Emphasis added)
- 'Mean changes from baseline in LS Z-scores at nine months were [...] and [...], respectively'. (Emphasis added)
- 'Femoral neck changes from baseline in both cohorts were non-significant (P>0.05) at either nine or 24 months'. (Emphasis added)

Accordingly, Shire submitted that the press release did not misleadingly imply that the extension study was a head-to-head study.

Shire refuted the Panel's conclusion that it was not sufficiently clear from the press release that BMD was a pre-specified exploratory endpoint from which no confirmatory conclusions could be drawn, and that the press release was consequently misleading in breach of Clause 7.2.

The Panel's reason for concluding that it was not sufficiently clear from the press release that BMD was a pre-specified exploratory endpoint was apparently the fact that this was referred to 'only' once and 'towards the end' of the press release.

However, Shire submitted that the Panel had adopted an overly simplistic approach. Indeed, in considering the placement of the statement within the text, the Panel focused only on the fact that the word 'exploratory' appeared in the fifth paragraph, which the Panel implied was too late within the text to have any meaning for the reader. However, the Panel did not appear to have considered whether or not the statement was properly contextualised, which was the real issue at stake. In drafting the press release, Shire sought to tread the established path of discussing scientific data. Thus, having described the presentation of the data at the EWGGD and explained what BMD referred to, the press release set out the scientific method, study design, study results and data generated. In fact, the statement that BMD was evaluated as an exploratory endpoint was explicit, clear, and properly

contextualised, appearing in the paragraph of the press release devoted to reporting on the newsworthy results and describing the key scientific issues.

Shire submitted that the material part of the press release was only one page and disclosing the nature of the endpoint more than once was repetitive and unnecessary. There was thus no reason to state numerous times that the endpoint was exploratory. The purpose of the press release was to convey newsworthy information in a succinct manner, avoiding repetition. The press release was clearly designed to be read in its entirety by its intended readership (the investor community, as well as relevant scientific and medical media), who could be relied upon to read the single page of text from beginning to end and draw the appropriate conclusions.

As regards the Panel's criticism that there was no explanation that confirmatory clinical conclusions could not be drawn from data derived from an exploratory endpoint, Shire disputed that this was necessary or appropriate. Shire emphasised that the readers of the press release would be well aware that confirmatory conclusions could not be drawn from an exploratory endpoint; it was not the purpose of such a press release to explain the basic principles of scientific data analysis to a specialised audience which was equipped to draw the appropriate conclusions. As the Panel stated (Point 2), 'Given the exploratory nature of the BMD analysis it was self evident that the studies were not powered to provide confirmatory findings on BMD'. As this consideration was, by the Panel's own admission, 'self-evident', then it was legitimate to assume that it would be understood as such by the readers of the press release, especially given that the press release stated this important fact in the place where readers would naturally focus and expect to see the key study limitations noted. There was nothing in the press release which contradicted the obvious fact that confirmatory claims/comparisons could not be based on an exploratory endpoint. The Panel's vague assertions that the press release 'invited the reader to draw such conclusions' (ie confirmatory clinical conclusions) (ruling 1b), and that it gave the 'impression' that the studies were powered to provide confirmatory findings on BMD (Point 2), were unfounded and inconsistent with the Panel's own statement that the correct interpretation of the data was 'self evident'.

Shire refuted the Panel's conclusion that the press release was not a fair reflection of the data in breach of Clause 7.2.

Shire submitted that as regards the presentation of the data, it was necessary to address the Panel's comment that certain statements in the press release were, in its view, 'unequivocal', and that this was inappropriate considering the 'limitations of the data'. Shire disputed that the language of the press release was unequivocal as stated previously the one page press release to be read in its entirety by a knowledgeable audience and both the relevant data and its exploratory nature were clearly stated therein. However, before considering this point further it was necessary to evaluate the 'limitations' of the data which the Panel focussed on.

- The 'limitations' of the data

Shire stated that it appeared that the Panel had referred to its comments that:

- There were imbalances between the two treatment arms at baseline. In this context, there was an implicit criticism of the fact that the press release referred to 'the more closely matched median baseline figures of -1.46 and -0.86, respectively' (i.e. as opposed to the mean figures of -1.56 in the VPRIV group and -0.57 in the Cerezyme group). As previously noted by Shire, Genzyme's conclusion that patients with normal BMD generally would not increase BMD levels at a significant rate above normal appeared to be inconsistent with its own data published by Wenstrup *et al*, 2007.

- The additional analyses adjusting for baseline lumbar spine bone status reduced the number of patients in each treatment arm, with '… only 4 patients in the Cerezyme group and more than double that in the VPRIV group.' (Panel's wording).

Shire submitted that in regard to the first point, imbalances between randomised groups were not uncommon for exploratory endpoints for which there were not endpoint-specific selection criteria or stratification at the time of randomisation. It was regrettable that the Panel had not considered the detailed explanation in Shire's response to Genzyme's complaint regarding the use of mean/median data. As Shire set out in its response to Genzyme's complaint it was important to clarify that the presentation of the median baseline lumbar spine Z-scores within each group allowed for a fair presentation of the central value (50% above; 50% below) and was not influenced by outlying values as in the case with the mean. Whilst both median and mean baseline scores were presented in the poster, the decision to use the median baseline Z-scores in the press release took into account the fact that there was not a normal distribution of baseline Z-scores.

This was entirely consistent with good statistical practice; the way in which the Panel tacitly criticised the use of median baseline figures without commenting at all on Shire's argument for the legitimacy of that approach was unfair. Without proper reasoning from the Panel, Shire could not fully defend the basis for the press release.

As regards the second point, the Panel tacitly criticised the fact that there were nine patients in the VPRIV group but 'only' four in the Cerezyme group, and wrongly implied that this sub-group analysis (in patients with a baseline lumbar spine Z-score <-1 or T-score <-1) was the entire basis for the press release. This sub-group data was presented in the poster, but not in the press release, and the purpose

of the analysis was to assess consistency (which was in fact demonstrated). Regrettably, the Panel did not appear to have engaged with Shire's detailed explanation of the patient sample size in the context of an orphan condition, or the rationale for conducting additional analyses in this sub-group. It was important to reiterate that:

- All adult patients completing the original study (HGT-GCB-039) were enrolled in the extension study (HGT-GCB-044). Paediatric patients were excluded from the BMD analysis as per the study protocol and current clinical practise.
- Of the total group of 24 patients, 13 were in the VPRIV arm and 11 in the Cerezyme arm.
- 5 patients out of the group of 24 were on concomitant bisphosphonate therapy and therefore excluded from the analysis (in accordance with the standard scientific approach in order to evaluate the efficacy of enzyme replacement therapy on bone).
- The entire remaining group of 19 patients (11 in the VPRIV arm and 8 in the Cerezyme arm) was analysed and reported in the press release.
- The data reported in the press release was confirmed by a subgroup analysis in patients with a baseline lumbar spine Z-score <-1 or T-score <-1, as reported in the poster only.

The Panel had thus given a misleading impression of the data and cast doubt on it. Shire emphasised however, that this was valid and newsworthy data, as supported by the fact that it was independently peer reviewed and accepted for presentation at the EWGGD. Indeed, in this rare disease area, data on 19 randomized patients was considered scientifically important to be shared with the investor community, as well as relevant scientific and medical media. Consistent with this, Shire had submitted the data to the European Medicines Agency in support of a Type II variation application to include new bone statements in the VPRIV SPC.

- The allegedly 'unequivocal' language

Shire submitted that the Panel had no justification for its dismissive approach to the data. It was in this context that the Panel's criticism of the 'unequivocal' nature of certain statements must be addressed. As explained above, the press release clearly stated that BMD was evaluated as an exploratory endpoint. Therefore, the title and subheading of the press release must be understood in this context and could not be read in isolation as the Panel implied. This was in obvious contrast with Case AUTH/2402/4/11 where titles of press releases were used in isolation as tweets.

Shire submitted that the statistical analysis presented in the poster and reflected in the press release was robust. In particular, no comparison was drawn between treatment arms precisely because, as noted by the Panel, exploratory endpoints could not be used as the basis for a robust comparison of medicines. The title and subheading of the press release did not contradict this: the title referred only to VPRIV ('Shire's VPRIV (velaglucerase alfa for injection) Showed Significant Improvement in Gaucher-Related Bone Disease'); and the subheading, by referring to improvement in BMD, also made clear that the analysis was 'within group' ('In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months').

Finally, as regards the Panel's comment that insufficient information had been provided to enable readers to properly assess how much weight to attach to the findings, Shire referred to its submissions above. Shire reiterated that the press release was clear regarding the exploratory nature of the analysis and further that the intended readership (the investor community, as well as relevant scientific and medical media) would be fully aware that while the data was clinically meaningful and hypothesis raising, confirmatory conclusions could not be drawn from such an endpoint.

Accordingly, Shire submitted that the press release was a fair reflection of the data.

**RESPONSE FROM GENZYME**

- General comments

Genzyme did not comment exhaustively on every element of Shire's grounds for appeal. Genzyme's response focused on the elements of Shire's appeal that it believed were of key importance for the assessment by the Appeal Board, including the claims that the press release:

- was not promotional;
- did not breach Clauses 7.2 and 7.3;
- did not breach Clause 22.2;
- was not subject to the requirement for mandatory certification;

and

- The claims that there was no breach of Clause 2 and
- The claims that Clause 1.8 was not capable of being breached.

Genzyme noted that it did not, as Shire suggested, challenge the conveyance of objective scientific information through press releases. Neither was it asking the Appeal Board to restrict this type of legitimate communication. Rather, Genzyme's principal argument was that the press release made comparative and superiority claims that overstepped the boundaries of objective scientific exchange. Genzyme also argued that the content of the press release was promotional, misleading, unfair and unbalanced and thus in breach of the Code. Moreover, although Genzyme focused its complaint and appeal on the press release, this should not be interpreted as a concession on the broader point, as Shire submitted in its appeal, that the data summarised in the underlying poster was scientifically valid. Genzyme reserved the right to challenge the poster itself in other forums.

- Non-promotional nature of the press release

Genzyme noted that the introduction to Shire's appeal indicated that the arguments on which the appeal was founded were based partly on the Panel's ruling that the press release was not promotional. Genzyme disagreed with this underlying premise. As stated in Genzyme's appeal, the Panel's ruling that the press release was non-promotional contradicted the Code, the previous practice of the Panel and the case law of the Court of Justice of the European Union.

Genzyme noted that Clause 1.2 of the Code defined promotion as '…any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines.' Although Genzyme acknowledged that many industry press releases conveying objective scientific information were not promotional, whether a particular press release was promotional turned on the totality of the circumstances, including the content of the release and the nature of its distribution. Genzyme cited Cases AUTH/2355/9/10 and AUTH/2201/1/09, in support of this proposition. Genzyme also referenced the ruling of the Court of Justice of the European Union where the court concluded that any information regarding the properties or availability of a medicine which was intended or likely to influence, either directly or indirectly, the behavior of patients or members of the public constituted promotion of this medicine.

Genzyme alleged that the press release went well beyond the recitation of objective scientific data by making broad and unequivocal product and superiority claims. This fact was noted by the Panel in its ruling. The Panel also noted that the press release was distributed widely to members of the public and patients, and that the press release: '…was likely to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine'.

For all of these reasons, Genzyme considered that Shire's press release was promotional.

- Points 1 and 2 - Breaches of Clause 7.2

Genzyme noted that Shire had made a number of arguments against the Panel's ruling that the press release breached Clause 7.2. As set forth further below, Shire's arguments on appeal were directed towards rather inconsequential points in an attempt to distract from the key point, that the press release included misleading and unfair comparative and superiority claims.

First, Genzyme noted that Shire argued that the press release was not misleading because the BMD data presented were obtained partly from an original head-to-head study. Shire's response missed the point. Although the data described in the press release were from an extension study and the original head-to-head study of several primary and secondary endpoints, BMD was neither a primary or secondary endpoint. As explained in Genzyme's complaint, BMD was measured as an 'exploratory' endpoint. The VPRIV and Cerezyme subgroups were not controlled for baseline BMD measures and, consequently, could not be studied with respect to this measure in a head-to-head manner. In fact, Shire acknowledged this point in its appeal. This supported Genzyme's argument that the key data presented in the press release were not generated in a direct head-to-head comparison and that this made the prominent and unqualified subheading of the press release unfair, unbalanced and misleading.

Genzyme disagreed with Shire's argument that the press release was not misleading because it disclosed that BMD was a pre-specified exploratory endpoint in an explicit, clear and properly contextualised manner. The statement in question appeared only once in the press release and, as noted by the Panel, was buried toward the end of the press release and was not accompanied by any explanation or discussion of the implications. In such circumstances, Shire's press release with its unequivocal headings and subheadings, created a misleading impression regarding the scientific value and implications of the BMD analysis.

Genzyme further noted that Shire's appeal claimed that the data in the press release was independently peer-reviewed and accepted for presentation at the EWGGD meeting, and that this supported its argument that the press release was fair and balanced. Although the poster presented by Shire at the EWGGD was peer-reviewed and accepted for presentation, the press release was not. Moreover, the presentation of the data in the press release was not identical to that in the poster. The press release went well beyond a recitation of the scientific findings contained in the poster by making unequivocal comparative and superiority claims.

Finally, Genzyme disagreed with Shire's submission that the subheading of the press release, 'In a head-to-head trial between VPRIV and Cerezyme' (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months', 'made clear that the analysis was "within group".' The subheading of the press release did not make such a clarification. Nothing in the press release would permit the members of the public to whom the press release was directed to interpret the subheading as stating that the BMD analysis was performed 'within groups.'

Genzyme concluded that agreement with Shire's arguments on any one of these points, would still not cure the overwhelming and misleading impression the press release gave that VPRIV outperformed Cerezyme in BMD improvements in a head-to-head analysis. The key point remained that Shire's press release overstepped the proper bounds of the legitimate exchange of scientific information and did so in a misleading, unfair and unbalanced manner.

**APPEAL BOARD RULING**

The Appeal Board noted the press release was based upon the poster presented at the EWGGD in Paris in June 2012 titled 'Bone Mineral Density Response to Enzyme Replacement Therapy Over 2 Years in Adults

with Type 1 Gaucher Disease'. The Appeal Board noted from the statistical analysis section in the poster that 'As the assessment of BMD using DXA in the study protocols of HGT-GCB-39 and HGT-GCB-44 was pre-specified as exploratory, there were no pre-specified hypotheses'.

The Appeal Board did not accept Shire's submission that the press release made no comparative claims. The Appeal Board noted that the prominent subheading of the press release read 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months'. In addition, the fourth paragraph of the press release stated 'Results from a head-to-head Phase III Study (HGT-GCB-039) of VPRIV and Cerezyme, and follow-on extension trial (HGT-GCB-044) of VPRIV, demonstrate a statistically significant improvement in lumbar spine (LS) BMD in Gaucher patients starting at nine months of treatment with VPRIV ($p<0.05$)'. The Appeal Board considered that, overall, it was not clear that the extension trial (HGT-GCB-044) had compared BMD results for VPRIV and Cerezyme to baseline and was not a head-to-head, between group comparison of VPRIV and Cerezyme. The Appeal Board considered that this was misleading and it upheld the Panel's ruling of a breach of Clause 7.2. Shire's appeal on this point was unsuccessful.

The Appeal Board considered that the press release, in particular the bold title and prominent subheading, implied that confirmatory results had been presented. Only once in paragraph five towards the end of the press release did it state that 'BMD, evaluated as an exploratory endpoint in the Phase III and extension studies, …' and this was insufficient to negate the overall impression that confirmatory clinical conclusions could be drawn. The press release was not sufficiently clear. The Appeal Board considered that the press release was thus misleading and upheld the Panel's ruling of a breach of Clause 7.2. Shire's appeal on this point was unsuccessful.

The Appeal Board noted from the poster that because there were no specific bone-related inclusion or exclusion criteria in the protocols for the studies and the randomization was not stratified by BMD, there were imbalances between the two treatment arms at baseline. The mean lumbar spine BMD Z-score in the VPRIV group was -1.56 and -0.47 in the Cerezyme group (the press release presented median values of -1.46 and -0.86, respectively). In the group of patients who did not receive bisphosphonates 2/11 had normal bone in the lumbar spine in the VPRIV group compared with 4/8 in the Cerezyme group. The Appeal Board noted that the patient numbers had not been included in the press release and considered that it would have been helpful if they had been, especially given the small number of patients in the studies (VPRIV n=13, Cerezyme n=11 and after adjustments to exclude patients with a baseline lumbar spine Z score of <-1, VPRIV n=8 and Cerezyme n=4). The Appeal Board noted Shire's acknowledgment at the appeal that the observed effects might be caused by type II statistical errors. The Appeal Board considered that overall the press release had not provided sufficient information for the reader to assess what weight to attach to the findings. The press release was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. Shire's appeal on this point was unsuccessful.

**2 The information, claims and comparison were based on unsound statistics**

**COMPLAINT**

Genzyme noted that Shire reasserted that no direct comparisons were made or intended, and that the information and claims presented did not breach the supplementary information to Clause 7.2. More specifically, Shire referred back to its arguments regarding breach of Clause 7.2 in asserting that the press release was based on sound statistics because the sample size was sufficiently powered, and the imbalance in baseline Z-scores did not impact the results. In addition, Shire explained that the purpose of a press release was to provide factual and balanced information (and not uninformative data), and that the data for femoral neck was given little prominence because it was not statistically significant.

Genzyme strongly disagreed with Shire's presumption that the press release contained no comparisons. Article 2(c) of the EU Directive on misleading and comparative advertising, the provisions of which were reflected in Clause 7.2 of the Code, defined comparative advertising as 'any advertising which explicitly or by implication identifies a competitor or goods or services offered by a competitor'. Moreover, Clause 7.2 of the Code specifically stated that, 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis'.

Consistent with this position, the PMCPA had, on numerous occasions, found comparative claims between medical products to constitute a breach of the Code. Specifically, the Shire press release at issue included a sub-headline which stated that, 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months' (emphasis added). Paragraph 5 of the Shire press release also described how the clinical study showed 'clinically and statistically significant improvement from baseline in mean [lumbar spine] Z-score … at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme' (emphasis added). Moreover, paragraph 5 also presented, in direct proximity, data from patients treated with VPRIV and patients treated with Cerezyme. It was indisputable that the totality of these claims conveyed the message that based on the data, VPRIV offered a clinical advantage over Cerezyme.

Moreover, the comparisons were misleading because the data was based on incorrect statistical methodology, as described in more detail below.

Genzyme repeated that a properly designed clinical study might have a small sample size but be sufficiently powered for statistical significance. However, since the BMD analysis was exploratory, Shire's studies were not designed to be sufficiently powered for this analysis. In addition, even assuming that the original study was sufficiently powered for this exploratory endpoint, the BMD analysis was based on a subgroup of a subgroup. Consequently, this retrospective BMD subgroup analysis was insufficiently powered to draw statistically significant conclusions.

Genzyme noted again that, at baseline, patients in the VPRIV group had a greater BMD deficiency than patients in the Cerezyme group. This was an important and meaningful discrepancy between the two groups with regard to the proportion of patients with 'normal' BMD. Patients who began with normal BMD generally would not increase BMD levels at a significant rate above normal. Thus, patients using VPRIV on average had significantly more room for improvement in BMD levels. Accordingly, the conclusion made in the press release, that patients on VPRIV showed more improvement in BMD compared with patients on Cerezyme, was based on patients who started from different baselines who had different capacities to improve and who might improve at different rates as a result. In fact, had Shire adjusted properly for baseline differences, patients using Cerezyme might have demonstrated a greater percentage improvement in BMD than patients using VPRIV.

While Shire acknowledged the imbalances with baseline lumbar spine Z-scores, it asserted that the results were robust because it had obtained similar results after adjusting for this difference. However, the results after adjusting for this difference were from a 'within-group' analysis, which could not support comparative/superiority efficacy claims. Furthermore, after adjusting for the difference in baseline lumbar spine Z-scores, the data was based on several subgroup analyses, and was not sufficiently powered. As such, the imbalances between the two treatment arms were not adequately addressed during the analysis and any comparisons of change from the baseline were not statistically valid.

In addition, the main data advertised by the press release – the difference in mean changes from baseline in lumbar spine BMD Z-score of the two treatment groups – was neither statistically valid nor reliable. The 95% confidence intervals covered a wide range of possible mean changes in BMD. In other words, individual patient responses to the two medicines varied widely, and the distribution of these patient responses overlapped. Given that the confidence intervals for the VPRIV and Cerezyme patient groups contained a significant amount of overlap, it was likely that there was no statistical difference between the two groups. Thus it could not be concluded that the mean changes in BMD were different, as opposed to being a result of mere chance. In other words, given that there was no significant difference between the groups for the outcomes measured, no conclusion regarding comparative effectiveness or superiority could be drawn.

Genzyme stated that, as Shire agreed, a press release must provide factual and balanced information. However, it was unbalanced to selectively present lumbar spine Z-scores. In addition, conclusions of product superiority based on exploratory endpoints must be adjusted for multiple endpoints in order to obtain a valid statistical significance. Even though the superiority claims made by the press release were based on multiple endpoints as well as an exploratory endpoint, the press release failed to disclose that this statistical adjustment was not made. Correcting for these multiple endpoints, a proper statistical analysis would not show improvement in VPRIV.

Genzyme alleged that, for the reasons above, the press release presented the poster data in a manner that misleadingly suggested that this was a like-for-like comparison based on a prospectively designed study devised to evaluate BMD as a primary endpoint in breach of Clause 7.2.

**RESPONSE**

Shire referred to the introductory section to its response to Point 1 above, which set out in detail the fact that no comparisons were drawn between treatment arms. This addressed the arguments raised by Genzyme. Shire therefore turned directly to the three specific points raised by Genzyme regarding alleged incorrect statistical methodology.

- Patient sample size

Genzyme repeated the same arguments raised under Point 1, as addressed above.

For the avoidance of doubt, Shire agreed that an exploratory endpoint was not designed to claim superiority and Shire never made such confirmatory claims; nor did it imply or intend such a message. Furthermore, since no confirmatory claims were being made, it was common practice and appropriate to assess statistical significance for exploratory endpoints without adjusting for multiple study endpoints. In its analysis, Shire had included all adults (n=24), as per the study design; children were not scheduled for DXA scans. Shire reiterated that it did perform a subgroup analysis of the adult population in the patients who did not receive concomitant bisphosphonates (n=19); this was an important subgroup to analyze as it provided an unadulterated estimate of ERT's treatment effect without concomitant medication for bone (biphosphonates). Results obtained by this subgroup analysis were similar when including the total group (n=24).

- Differences in BMD deficiency between treatment arms

Shire submitted that Genzyme largely repeated part of Point 1, which Shire had already addressed above.

Genzyme further claimed that 'the main data advertised by the press release – the difference in mean changes from baseline in lumbar spine BMD Z-score of the two treatment groups – was neither statistically valid nor reliable'. Shire submitted that once again, however, Genzyme misrepresented what constituted the 'main data' communicated in the press release. There was no 'advertisement' or comparison made, implied or intended between the two groups in either the poster presentation or the press release; the purpose of the press release was to report on the fact that the data demonstrate that VPRIV improved Gaucher-related bone disease by a sustained increase in BMD. As already explained, the nine-month mean change from baseline observed with VPRIV was consistent with the lumbar spine BMD improvements seen in Shire's published Phase I/II clinical trial TKT025EXT (Elstein *et al*) and the other naïve Phase III clinical trial (TKT032). The press release also reported on the improvement from baseline in patients treated with Cerezyme, consistent with the poster. As also explained above, the nine-month mean change from baseline (+0.06 without concomitant bisphosphonates; 0.10 including patients on concomitant bisphosphonates) observed with Cerezyme was consistent with the lumbar spine BMD improvements reported in the literature (+0.13/year; 0.09 at nine months; Wenstrup *et al*). Shire rejected Genzyme's assertion that the data was neither valid nor reliable.

- Presentation of lumbar spine Z-scores

Shire submitted that Genzyme largely repeated part of Point 3 which Shire had already addressed above.

As mentioned above, the press release specifically presented data from Study 039 as an exploratory endpoint. It also made factual statements from the additional comprehensive data that were prospectively collected across the clinical trials program (which formed the basis for the poster presentations at EWGGD). It was common practice to communicate data from clinical trials that were prospectively carried out.

There were no claims or suggestions of product superiority in either the poster or the press release, and as such it would not make sense to complete adjustment for multiple endpoints in order to obtain valid statistical significance for such a comparison.

Shire submitted that its statistical methods and analyses were sound. The distribution of the within patient changes from baseline to nine months were normally distributed (bell shaped; mean ~ median). As a result, the mean change from baseline to nine months and the corresponding 95% confidence intervals were presented.

In summary, the press release was factual and appropriately referenced the EWGGD scientific poster presentations. It clearly stated that the results, obtained from data collected prospectively, were based on an exploratory endpoint. No confirmatory claims were made, implied or intended.

In summary, Shire submitted that the information in the press release was based on sound statistics, in compliance with Clause 7.2 and its supplementary information.

In response to a request to comment on the confidence intervals depicted in Figure 2 of the poster on which the press release at issue was based, in relation to statistical significance, Shire submitted that there was a direct mathematical link between the p value and the confidence interval:

- If the p value was < 0.05 then the 95% confidence interval for the mean change from baseline would exclude zero, where zero equals no effect, and vice versa
- If the p value was > 0.05 then the 95% confidence interval for the mean change from baseline would include zero and vice versa
- If the p value equaled 0.05 then one end of the 95% confidence interval would be equal to zero; this was the boundary between the conditions above
- The important element that made the link work was the correspondence between the significance level 5% and the confidence coefficient 95%.

Shire submitted that in the poster on which the press release was based, Figure 2 depicted the mean within-group change from baseline to 9 months and the mean within-group change from baseline to 24 months separately for each group. At 9 months the lower bound (0.10) of the 95% confidence interval for the mean within-group change from baseline for the VPRIV cohort was above zero which was consistent with a p value <0.05; the 95% confidence interval was [0.10, 0.55]. At 9 months the lower bound (-0.22) of the 95% confidence interval for the mean within-group change from baseline for the Cerezyme cohort was below zero which was consistent with a p value >0.05; the 95% confidence interval was [-0.22, 0.34]. However, a p value told one nothing about clinical importance. In Shire's view, the most appropriate way to provide the information was by presenting the mean changes together with confidence intervals as provided in Figure 2 of the poster.

Shire stressed once again that there was no comparison between the two treatment groups made or intended to be made in the press release. The answer to the question whether one could judge if the 9 month mean change from baseline between the two treatment groups was significantly different depending on whether or not the 95% confidence intervals overlapped, was 'not always'. If two individual means had non-overlapping 95% confidence intervals, they were necessarily significantly different. However, the converse was not true. A significant p value did not necessarily correspond to non-overlapping 95% confidence intervals for the individual means. In other words, if two individual means had overlapping 95% confidence intervals, it was not necessarily true that they were not significantly different. Confidence intervals associated with statistics (eg means) could overlap as much as 29% and the statistics could still be significantly different (van Belle 2002). In other words, the overlap could be surprisingly large and

the statistics still significantly different. In summary, it was erroneous to determine that statistical significance of the difference between two statistics (eg means) based on overlapping confidence intervals.

**PANEL RULING**

The Panel considered that Shire's assertions that the press release contained no direct comparisons between VPRIV and Cerezyme and that no confirmatory claims were stated or implied were disingenuous. It noted its comments at Point 1 above in this regard. The original study from which baseline measurements of BMD were taken was a head-to-head non-inferiority study of VPRIV and Cerezyme in type 1 Gaucher disease, the primary endpoints of which were unrelated to BMD. The subheading of the press release stated that in a head-to-head trial between VPRIV and Cerezyme, only those treated with VPRIV experienced a statistically significant improvement in lumbar spine BMD at 9 months. The press release went on to state that a statistically significant improvement from baseline in mean lumbar Z-score was seen at 9 months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme.

The Panel noted each party's submission about baseline BMD measurements and sample size. It noted its general comment about the press release at Point 1. Given the exploratory nature of the BMD analysis it was self evident that the studies were not powered to provide confirmatory findings on BMD. The press release gave a contrary impression. Ultimately the allegations on this point were inextricably linked to Point 1 above and the Panel considered that its ruling of a breach of Clause 7.2 applied equally here. This ruling was appealed by Shire.

**APPEAL BY SHIRE**

Shire noted that the Panel considered that the issues at stake under Points 1 and 2 were inextricably linked and Shire had addressed them together at Point 1 above.

**RESPONSE FROM GENZYME**

Genzyme referred to its submission in response to Shire's appeal at Point 1 above.

**APPEAL BOARD RULING**

The Appeal Board did not accept Shire's submission that the press release made no comparative claims. The Appeal Board considered that the press release reported an exploratory endpoint in such a way as to imply a robust clinical result. This was misleading. The Appeal Board agreed with the Panel's view that the allegations on this point were inextricably linked to Point 1. The Appeal Board noted its comments and rulings at Point 1 above wherein it had upheld the Panel's ruling of a breach of Clause 7.2. The Appeal Board considered that that ruling also applied here and thus the appeal on this point was unsuccessful.

**3 Misleading comparisons with Cerezyme**

**COMPLAINT**

Genzyme noted that Shire asserted yet again that there was no direct or intended comparative/superiority claim involving VPRIV and Cerezyme. It further argued that 'Each of VPRIV and Cerezyme is compared to its respective baseline and therefore there is no breach of Clause 7.3'.

Genzyme alleged that to argue that the press release contained no comparative/superiority claim simply ignored the plain language of the document. Moreover, as described in detail in above, this comparison was not balanced. It was unfair, unbalanced, not based on an up-to-date evaluation of all the evidence and based upon unsound statistics. All these elements underscored the misleading nature of the comparative/superiority claims in the press release in breach of Clause 7.3.

**RESPONSE**

Shire submitted that Genzyme's allegation that the press release was misleading in breach of Clause 7.3, was premised on its preceding allegations (Points 1 and 2) that the press release was unfair, unbalanced, not based on an up-to-date evaluation of all the evidence and based on unsound statistics. Shire considered that, its response to Points 1 and 2 above, soundly dismissed Genzyme's arguments. Accordingly, it must be concluded that the press release was not misleading. In particular, it must be reiterated that the press release did not contain any comparative/superiority claim; it objectively reported the data presented in the EWGGD poster presentation which Genzyme did not object to.

**PANEL RULING**

The Panel noted its comments and rulings above at Points 1 and 2 about comparisons in the press release between VPRIV and Cerezyme in relation to BMD results. The Panel considered that the press release implied that the studies cited had produced robust confirmatory comparative data that VPRIV significantly improved lumbar spine BMD and that Cerezyme did not. This was not so. The data was such that no conclusive comparisons could be made. The comparison was misleading and a breach of Clause 7.3 was ruled. This ruling was appealed by Shire.

**APPEAL BY SHIRE**

Shire referred to its general comments made it its appeal at Point 1 above.

Shire refuted the Panel's conclusion that the press release drew a misleading comparison by wrongly implying that the studies had produced robust confirmatory comparative data that VPRIV significantly improved lumbar spine BMD and that Cerezyme did not.

The press release did not draw explicit or implicit comparisons between VPRIV and Cerezyme. As

explained in detail in Shire's response above, improvement in BMD from baseline was separately assessed within each treatment group. Patients within the VPRIV group showed a statistically significant improvement from baseline after 9 months. Patients within the Cerezyme group did not show a statistically significant improvement from baseline after 9 months. The statements in the press release quoted by the Panel in support of its conclusion that the press release made comparative claims actually demonstrated the opposite, namely that the two cohorts of patients were treated separately: 'Clinically and statistically significant improvement from baseline in mean LS Z-score was seen at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme'. This was simply a factual reflection of the study, the results of which had not been disputed. It would be misleading and inaccurate not to mention the results obtained in the Cerezyme cohort in the press release.

Further, as explained above, it was manifestly clear in the press release that BMD was assessed as an exploratory endpoint and that the data were not confirmatory.

Therefore, Shire submitted that the Panel's assertion that the press release implied that the studies produced robust confirmatory comparative data was entirely without foundation. Shire appealed the Panel's ruling of a breach of Clause 7.3.

**RESPONSE FROM GENZYME**

Genzyme referred to its general comments made in response to Shire's appeal at Point 1 above.

Genzyme noted that Shire had claimed in its appeal that the press release did not breach Clause 7.3, which prohibited misleading comparisons, because, put simply, it did not draw any explicit or implicit comparisons between VPIRV and Cerezyme. This was directly contradicted by the press release's subtitle that, 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months'. Shire's claim that the improvement in BMD from baseline was separately addressed in each treatment group did not cure the overwhelming impression created by the press release that VPRIV outperformed Cerezyme on BMD measures in a head-to-head comparison. The Panel agreed with Genzyme on these points, concluding in its ruling that Shire's arguments that the press release did not make comparative or superiority claims were 'disingenuous'.

**APPEAL BOARD RULING**

The Appeal Board noted its comments and rulings at Points 1 and 2 above. The Appeal Board considered the press release, in particular the title and subheading, compared VPRIV with Cerezyme and implied that there was confirmatory evidence that VPRIV significantly improved lumbar spine BMD and that Cerezyme did not. The evidence, however, was insufficient to make such a comparison and the press release was misleading in this regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.3. Shire's appeal on this point was unsuccessful.

**4 Promotion to the public and encouraging members of the public to ask their health professional for a prescription only medicine**

**COMPLAINT**

Genzyme noted that Shire did not consider the press release was promotional and that it was not intended to encourage members of the public to ask their health professional to prescribe VPRIV. Lastly, Shire stated that, '[i]n any event, the information contained in the press release is factual and presented in a balanced way'.

Genzyme disagreed with this. As detailed above, the press release was promotional and was intended for dissemination to patients and to the public in breach of Clause 22.1. Moreover, Shire's assertion that press release was directed at, and intended for review by, investors and scientific media only was false given placement of the press release on its global website, distribution by Shire UK agents to the patient group for Gaucher disease in the UK and publication by various UK and European newswires. As such, the press release advertised a prescription only medicine to the public in breach of Clause 22.1.

In addition, the press release did not present the study data in a balanced manner. The comparative/superiority efficacy claims were misleading and unsubstantiated and gave the inaccurate impression that VPRIV would more successfully treat Gaucher-related bone disease than Cerezyme, thereby raising unfounded hopes among Gaucher patients in breach of Clause 22.2. The press release included a sub-headline stating that, 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months' (emphasis added). Paragraph 5 of the press release also described how the clinical study showed 'clinically and statistically significant improvement from baseline in mean [lumbar spine] Z-score … at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme' (emphasis added). Moreover, Paragraph 5 went on to present in direct proximity data from patients treated with VPRIV and patients treated with Cerezyme. Genzyme alleged that, taken together, these claims conveyed a message that VPRIV offered a clinical advantage over Cerezyme. This was supported by the various headlines used by the UK and European publications that covered this story and discussed above.

Finally, given that this press release was widely distributed in the UK by Shire's public relations agencies, Genzyme alleged that Shire had failed to comply with Clause 22.5.

**RESPONSE**

Shire submitted that for the purposes of Clause 22, the 'public' included patients, the more general

public (for example journalists, shareholders and employees of pharmaceutical companies) and the wider scientific community (within which patient organisations play an important role in this orphan disease area). Each of these categories of person was specifically mentioned in the supplementary information to Clause 22. Clause 22.2 expressly allowed the provision of information to the 'public', provided that it was factual, balanced, did not raise unfounded hopes of successful treatment, was not provided for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine and – moreover - did not constitute promotion.

Accordingly, the dissemination of non-promotional information to the 'public' in the broad sense outlined above (including proactive communications such as press releases and mailings to patient organisations, as mentioned in the supplementary information to Clause 22.2) was in principle acceptable. However, reading between the lines, it appeared that, from the scope of the distribution, Genzyme had tried to draw the conclusion that the press release was promotional. Shire referred in particular to the following wording in Genzyme's complaint:

> 'Moreover, Shire's assertion that press release was directed at, and intended for review by, investors and scientific media only is false given placement of the press release on its global website, distribution by Shire UK agents to the patient group for Gaucher disease in the UK [...] and publication by various UK and European newswires. As such, the press release advertises a prescription only medicine to the public in violation of Clause 22.1 of the Code' (emphasis added).

Shire submitted that Genzyme's reasoning was circular. It could not be concluded that the press release was promotional on the basis of the scope of distribution; as explained above the Code specifically allowed non-promotional information to be disseminated to a broad variety of people (including patients, journalists, investors and patient organisations). Rather, as detailed in Shire's response to the allegation in Point 6 below, the press release was not promotional in nature.

Genzyme alleged that the press release breached Clause 22.2 because it did not present the study data in a balanced manner; the so-called 'comparative/superiority efficacy claims' were misleading and unsubstantiated thereby raising 'unfounded hopes among Gaucher patients'; and the press release was made for the purpose of encouraging members of the public to ask their health professional to prescribe VPRIV.

Shire refuted these allegations and referred to its response to allegations 3, 4 and 5 regarding the presentation of the study data, which was balanced, factual and not misleading. In particular, it should be noted that the press release reflected the poster presented at the EWGGD meeting, which Genzyme raised no objection to. As such, the press release could not raise unfounded hopes among Gaucher patients.

Further, Shire did not accept Genzyme's allegation that the purpose of the press release was to encouraging members of the public to ask their health professional to prescribe VPRIV. To reiterate, this was a scientific press release which presented newsworthy information in an objective and balanced manner. The language of the press release was measured and non-emotive. For example, it stated that:

> '[m]easuring BMD can help to quantify the impact of Gaucher disease on the patient's bone and can help identify the potential benefits of treatment in improving Gaucher-related bone disease' (emphasis added).

Further, Shire submitted that it was clear that BMD was evaluated as an 'exploratory endpoint'. It was very clear from its language that the press release was not issued to encourage members of the public to ask their health professional to prescribe VPRIV, nor would it raise unfounded hopes of successful treatment. It was provided to the Gauchers Association as an important member of the scientific community; it was not given to the association to encourage patients to seek a prescription for VPRIV. Further, providing the press release to the Gauchers Association would not have such an effect as the patient organisation was at liberty to decide how it wished to use any information provided to it, and whether it wished to add its own commentary. In the event, as explained further in the response to allegation 1, the Gauchers Association decided not to post the press release when it was given it by Shire's agent; instead the body of the press release was posted by the Gauchers Association more than a month afterwards and it included its own commentary on the data.

Shire agreed that it was responsible for information about its products that was issued by its public relations agencies. However, in the present case, Shire was satisfied that its agents acted appropriately in distributing the press release; in particular, its agents did not seek to influence the manner in which the material was subsequently presented (Shire referred further to its response to the allegation in Point 6 below).

Shire submitted that it carefully controlled the activities of its agents and required, under clause 2.3 of the master services agreement that:

'Service Provider shall provide Services to Shire as described herein, or in any Statement of Work, conscientiously and in a timely, competent and efficient manner, in accordance with the applicable professional standards currently recognized by such profession and devote its best efforts and abilities thereto. [...] In performing the Services, Service Provider shall comply with the applicable Statement of Work, this Agreement, the written instructions of Shire, standard operating procedures approved by

Shire, relevant professional standards and all applicable laws, rules and regulations as applicable to Service Provider or to the Services'.

Shire arranged a personalised training day for its PR agency on 25 August 2011 with the vice president of compliance. The training included a presentation on Shire's policies on the following areas:

- Working with patient organisations
- Advisory boards
- Donations, grants and sponsorships
- Company organised meetings
- Material approval.

This was followed in February 2012 by an update training session for all agencies. Through such training, Shire submitted that it ensured that its agents acted in a way which complied with the Code when undertaking any activity on Shire's behalf. Shire provided e-mail correspondence with its PR agency (25-26 August 2011) regarding the training session organised for it by Shire and copies of training declarations from the training sessions of August 2011 and February 2012.

**PANEL RULING**

The Panel considered that it was not unacceptable to make available information about prescription only medicines to patient organisations but its content and provision had to comply with the Code particularly Clauses 22 and 23 and the relevant supplementary information.

The Panel noted that Genzyme's allegation that the press release was promotional appeared to be based on the fact that a press release which contained information about a prescription only medicine was distributed to a patient organisation. On this narrow point, and given its comments above, the Panel did not consider that the press release was promotional and ruled no breach of Clause 22.1. This ruling was appealed by Genzyme.

The Panel noted that Clause 22.2 required that information about prescription only medicines which was made available to the 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. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.

The Panel noted its rulings above in relation to the misleading statements made about VPRIV in relation to BMD and considered that the press release had not presented information about VPRIV in a balanced way. The press release was likely to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. A breach of Clause 22.2 was ruled. This ruling was appealed by Shire.
The Panel noted Genzyme's allegation of a breach of Clause 22.5 in relation to the activities of Shire's PR agency and considered that this clause was a statement of principle in relation to a company's responsibilities under Clause 22; it was not capable of being breached and consequently no ruling was made.

**APPEAL BY GENZYME**

- General comments

Genzyme noted that the Panel's conclusion that the press release was not promotional underlied its ruling's of no breach of Clauses 4.1 and 22.1. Although Genzyme agreed that press releases were not *per se* promotional, it contended that the facts and circumstances of each press release should determine its treatment under the Code. In this case the press release went beyond the simple recitation of study results by making broad and unqualified claims about VPRIV's superiority over Cerezyme and VPRIV's effectiveness in treating BMD. The fact that the press release was picked up by public relations newswires and was affirmatively provided to a patient group was only one of the factors that should be considered in the analysis. Genzyme did not argue that Shire's distribution of the release to a UK patient group was determinative on this point. In light of Genzyme's arguments and of the Panel's rulings, there were strong arguments supporting a conclusion that the press release was promotional. This conclusion was also supported by the definition of promotion in Clause 1.2, in the previous rulings of the Panel, and the related case law of the Court of Justice of the European Union. Accordingly, Genzyme alleged breaches of Clauses 4.1 and 22.1.

Genzyme submitted that the rulings of no breaches of Clauses 4.1 and 22.1 hinged on whether the press release was considered promotional; Genzyme respectfully averred that it was. Many industry press releases conveying objective scientific information were indeed not promotional and, accordingly, Genzyme did not seek a broad categorical ruling about press releases. Genzyme agreed with Shire that whether a press release was promotional turned on the totality of the circumstances.

In this matter, Genzyme alleged that the press release went well beyond the scientific findings contained in the poster presented at the EWGGD meeting on 28-30 June. The press release also made unsubstantiated and misleading comparative claims as acknowledged by the Panel. The Panel also acknowledged that the press release was distributed widely to members of the public and patients. For these reasons, Genzyme alleged that the press release was promotional and its distribution constituted a promotional activity. The arguments supporting this position were outlined below.

- Clause 22.1

Genzyme noted that it had previously alleged that the press release was in breach of Clause 22.1, which stated that, 'prescription only medicines must not be advertised to the public'. As described above, Genzyme noted it had previously argued that the

distribution of the press release by public relations agents to newswires and a UK patient organisation constituted distribution of the press release to the members of 'the public' for purposes of Clause 22.

Genzyme stated that the Panel appeared to rule that the press release did not breach Clause 22.1 solely on the basis that it was not promotional. For all the reasons above the press release was promotional and was distributed to patients and members of the public in breach of Clause 22.1. This position was also supported by the Panel ruling in Case AUTH/2355/9/10. The Panel ruled in that case that a press release constituted promotion of a prescription only medicine to the public in breach of Clause 22.1 because it contained product-related claims, presented information in a non-balanced way, and encouraged members of the public to ask their health professional to prescribe the medicine.

In the present case, Case AUTH/2528/8/12, the Panel ruled that Shire's press release was likely to encourage patients to ask their health professional to prescribe VPRIV and that the press release did not present information about VPRIV in a balanced way. The Panel also noted on a number of occasions that the press release contained comparative and superiority claims in relation to VPRIV. It was, therefore, surprising that the Panel reached a different conclusion from that in Case AUTH/2355/9/10 and ruled that Shire's press release was not promotional.

**RESPONSE FROM SHIRE**

- General comments

Shire submitted that two issues were at stake in Genzyme's appeal: whether the press release was promotional in nature and whether it disparaged Cerezyme.

Genzyme largely relied on the Panel's conclusion that the press release was misleading in certain respects as the basis for its argument that the press release was promotional and disparaging. As set out in its own appeal, Shire strongly refuted the Panel's ruling that the press release was misleading (or otherwise in breach of the Code). However, and in any event, Shire submitted that the question of whether the press release was misleading was distinct from both whether it was promotional or whether it disparaged Cerezyme. Shire contended that the press release was not promotional or disparaging, for the reasons set out in this response and in Shire's original response to Genzyme's appeal.

- No breach of Clauses 22.1 and 4.1

Shire submitted that Genzyme's appeal of the Panel's ruling of no breach of Clauses 4.1 or 22.1 hinged on whether the press release was promotional. If it was not, as Shire contended and as the Panel agreed, then there could be no breach of Clause 22.1 (which prohibited promotion to the public) or Clause 4.1 (which required the prescribing information to be included in promotional material).

According to Genzyme, the content of the press release and its distribution 'to a wider audience' rendered it promotional. These arguments were addressed below. However, as Genzyme's appeal largely repeated its original complaint, Shire noted its original response where it explained in detail why the press release was non-promotional.

As a preliminary point, Shire noted that Genzyme had mistakenly referred to the revised definition of promotion in Clause 1.2 Second 2012 edition of the Code. That edition of the Code, however, did not come into operation until 1 July 2012 (with a transitional period until 31 October 2012). As the press release was dated 28 June 2012, the 2012 Code applied. The difference between the two definitions of promotion was as follows:

- 2012 Code: 'The term 'promotion' means any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines.'
- Code Second 2012 edition: 'The term 'promotion' means any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines.' (Additional language highlighted in bold)

Whilst Shire did not seek to suggest that Genzyme's entire argument on promotion depended on the broader definition in the Second 2012 edition of the Code, it was important to correct this point as the question at stake for the purposes of Genzyme's appeal on Clauses 4.1 and 22.1 was whether the press release constituted promotion within the narrower sense of the 2012 Code. Shire submitted that this consideration was relevant to the question of promotion to the public because, arguably, the broader definition (encompassing 'consumption' and 'use') would mean that more material was considered to be promotional in nature. In any event, Shire submitted that the press release did not fall within either definition of promotion set out above.

Genzyme further confused matters by referring again to the ruling of the Court of Justice of the European Union (Damgaard). However, Shire respectfully submitted that this was not relevant to the present case, where the press release must be considered in accordance with the Code and previous published PMCPA cases. The Damgaard test was 'intended or likely to influence', which was different from the test for promotion under the Code. However, and in any event, the press release did not constitute promotion under either test. Unlike the press release at stake in Damgaard, the VPRIV press release did not emphasise the virtues of the product, but objectively reported scientific data.

Shire noted that it, Genzyme and the Panel all agreed that press releases were not inherently promotional

in nature and that whether or not a particular press release was promotional was a question of fact (which depended on all the circumstances). Further, all three parties agreed that sending a press release to a patient organisation did not render otherwise non-promotional material promotional. In these circumstances, Shire submitted that Genzyme had not made a case as to why the press release was promotional.

- The content of the press release

One of Genzyme's main arguments was that the content of the press release was promotional because it was considered by the Panel to make misleading and unbalanced claims. Shire strongly refuted that the press release was misleading or unbalanced. However, even a finding that the press release was misleading or unbalanced did not render the content promotional; the two issues were distinct. Indeed, the essence of Genzyme's argument - that promotional material was material which was misleading and/or unbalanced – could not be correct. This was because the promotion of medicines was *prima facie* acceptable under the Code, provided that there was no promotion to the public, and the other requirements of the Code were met (including that the content was not misleading). Accordingly, the question of whether material was misleading was distinct from the question of whether that material was promotional or not.

Shire noted that Genzyme had alleged that the Panel was illogical to conclude that the press release was non-promotional, considering its ruling (contested by Shire) that it was likely to encourage patients to ask their doctor to prescribe VPRIV in breach of Clause 22.2. Conversely, in its appeal, Shire highlighted that it was contradictory for the Panel to conclude that the press release was likely to encourage patients to ask their doctor to prescribe VPRIV, considering that it had accepted it was non-promotional. Indeed, Shire explained that if Clause 22.2 was understood in terms of effect rather than intention, there would appear to be a logical disconnect within the Code itself (specifically, between Clause 1.2 on the one hand, which defined 'promotion'; and Clause 22.2 on the other). This supported Shire's argument that Clause 22.2 was specifically framed as a provision based on intention, rather than effect. Understanding it that way was consistent with the wording of the Clause itself ('Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine' - emphasis added), and it was also consistent with a logical and schematic interpretation of the Code.

In any event, it was clear from previous rulings of the Panel that a finding that statements were made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine was only one factor in the determination of whether the activity/material constituted promotion to the public. Therefore, whilst there were some cases where the Panel ruled a breach of both Clauses 22.1 and 22.2, there were others where the Panel concluded that the material was non-promotional, notwithstanding that it was made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine. For example, in Cases AUTH/1822/4/06 and AUTH/1823/4/06, the Panel concluded that an article which referred to study results as 'stunning' and 'exciting' would encourage readers to ask their health professional to prescribe Ferriprox, although it did not consider that the article constituted an advertisement to the public for a prescription only medicine.

In the present case, Case AUTH/2528/8/12, Shire strongly contested that the press release was promotional. It did not go beyond the scientific findings contained in the poster as Genzyme alleged. Rather, the press release accurately reflected the findings in the poster, and the level of information was appropriate for dissemination by way of a press release (namely, relevant and newsworthy information). In its appeal, Genzyme referred to Case AUTH/2201/1/09 and Case AUTH/2355/9/10 (also referenced in its complaint), which it argued supported the proposition that a press release could be promotional based on its content. Shire referred to its response to Genzyme's complaint, where it explained that those two cases were clearly distinguishable from the matter at issue. It should be noted that Case AUTH/2201/1/09 was not relevant to Genzyme's appeal of no breach of Clause 22.1 (prohibiting promotion to the public) as the case only concerned Clause 22.2 (encouraging members of the public to ask their doctor to prescribe a specific medicine). As regards Case AUTH/2355/9/10, Shire reiterated that the content of the press release in that case was not comparable with the content of the press release now at issue. The press release in that case was considered promotional principally because it contained 'very strong claims' (Appeal Board's description) that were also contrary to Clause 22.2, such as 'improve survival in childhood cancer', 'reduces the risk of death by almost one third', and 'save an additional eight lives each year'. In sharp contrast, the press release now at issue, clearly stated that the data were based on an exploratory analysis, and the scientific findings were described in neutral language. Accordingly, the press release did not promote the prescription, supply, sale or administration of VPRIV.

- The manner in which the press release was distributed

Shire noted that Genzyme had stated that it 'never intentionally argued' that the distribution of the press release was the key or only argument supporting the position that the press release was promotional. It appeared that Genzyme based its conclusion that the press release was promotional on the scope of distribution. Shire explained that Genzyme's reasoning was circular; it could not be concluded that the press release was promotional on the basis of the scope of distribution considering that the Code specifically allowed non-promotional information to be disseminated to a broad variety of

persons (including patients, journalists, investors and patient organisations).

Shire disagreed with Genzyme's assertion that in combination with the promotional content of the press release, its distribution to a wider audience constituted promotional activity. Shire maintained that the press release was inherently non-promotional in content and that sending it to a 'wider audience' (as arbitrarily defined by Genzyme) did not render it promotional. As noted in Shire's response to the complaint, the press release was provided to a newswire (a subscription-based 'pull' service for media), which was a standard communication route for investor releases. Shire reiterated that the intended audience of the press release was the investor community (potential and current), as well as relevant scientific and medical media. This included the media arm of the Gauchers Association, a patient organisation which had an integral role in the scientific community for Gaucher disease.

- Conclusions regarding Clauses 22.1

Shire maintained that the previous cases did not support Genzyme's claim that the press release was promotional. In these circumstances, and for all the reasons explained above and Shire's original response, it must be concluded that the press release was non-promotional. Accordingly, the Panel's ruling of no breach of Clause 22.1 should be upheld

**FINAL COMMENTS FROM GENZYME**

- General comments

Genzyme did not see that the use of the definition in the 2012 Code rather than the Second 2012 edition of the Code made any difference to the argument that the press release was promotional. In fact Genzyme argued that the press release fell within both definitions.

Genzyme alleged that the press release was promotional because it made claims about VPRIV's efficacy and comparative efficacy vs Cerezyme. The press release did not merely report the scientific findings contained in the poster presented at the EWGGD on 28-30 June, it promoted Shire's product. Even if the information in the poster was accurate (Genzyme strongly asserted that it was not accurate) the press release was promotional because it was taking its audience further than the poster did with (unsubstantiated) claims which positively compared Shire's product with Genzyme's product.

- Clause 22.2

Shire's argument that Clause 22.2 should be understood in terms of its intention rather than the effect it had (and could have) on the public, was flawed. Genzyme submitted that the spirit of the Code and the wording of Clause 22.2 were intended to capture both intention and effect of the act. Genzyme referred to Case AUTH/2322/9/10, in which the Appeal Board upheld the Panel's ruling that as the press release in that case contained very strong claims which were contrary to Clause 22.2, they were in effect advertisements aimed at the public and therefore contrary to Clause 22.1. The Appeal Board further held that, irrespective of whether members of the public read the press release, the fact that they could access it meant that it had the potential to encourage them to ask their health professional to prescribe the prescription only medicine in question.

Further Genzyme alleged that 'google alerts' picked up the press release; many Gaucher patients would be likely to have 'google alerts' on the disease and therefore would be very likely to have read this misleading press release.

**APPEAL BOARD RULING**

The Appeal Board noted its rulings in Points 1, 2 and 3 above where it had ruled that the press release had made misleading claims about VPRIV, and VPRIV vs Cerezyme based on limited exploratory data. The Appeal Board noted that the press release had been widely circulated including to a patient organisation. The Appeal Board noted that Clause 22.1 prohibited the advertisement of prescription only medicines to the public. The Appeal Board considered that the press release, although not an advertisement *per se*, did promote VPRIV and thus it ruled a breach of Clause 22.1. Genzyme's appeal on this point was successful.

**APPEAL BY SHIRE**

Shire referred to its general comments made in its appeal at Point 1 above.

Shire submitted that it appeared that there were two aspects to the Panel's ruling of a breach of Clause 22.2. According to the Panel the press release did not present information about VPRIV in a balanced way (contrary to the first sub-paragraph of Clause 22.2) and it was likely to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine (contrary to the second sub-paragraph of Clause 22.2). These two aspects of the Panel's ruling were contested in turn below.

- First sub-paragraph of Clause 22.2

Shire submitted that, the Panel's conclusion was expressed to follow-on from its rulings in relation to the misleading statements made about VPRIV in relation to BMD. However, Shire strongly disputed the Panel's ruling that the press release contained misleading statements or was in any way unbalanced (reference was made to Shire's appeal against the Panel's rulings of breaches of Clauses 7.2 and 7.3 above).

Shire submitted that if the Panel's rulings of breaches of Clauses 7.2 and 7.3, were overturned then this first aspect of the Clause 22.2 ruling automatically fell away.

- Second sub-paragraph of Clause 22.2

Shire submitted that the Panel was not empowered to rule a breach of Clause 22.2 on the basis that the press release was 'likely' to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. The second sub-paragraph of Clause 22.2 was specifically framed as a breach based on intention, rather than effect:

> 'Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.' (Emphasis added)

Shire submitted that accordingly, the Panel was entitled to rule a breach of the second sub-paragraph of Clause 22.2 only if it could be demonstrated that a company's purpose, ie intention in making a statement was to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. In the present case, Shire had no such intention, nor could such intention be inferred from either the content or the distribution of the press release.

Further, and in any event, Shire refuted the conclusion that the press release would have the effect of encouraging members of the public to ask their health professional to prescribe VPRIV. There was in fact a contradiction between the Panel's rulings: on the one hand, that the press release was non-promotional (Clause 22.1) and on the other, that it would encourage members of the public to ask their health professional to prescribe a specific prescription only medicine (Clause 22.2, second sub-paragraph). This reinforced the fact that Clause 22.2 was concerned with intention rather than effect; otherwise there would be a logical disconnect within the Code itself (namely, between the definition of 'promotion' in Clause 1.2 on the one hand, and the scope of Clause 22.2 on the other).

Cases where breaches of Clause 22.2 (second sub-paragraph) were ruled were typically those where the material in question contained very positive statements about a particular product (whether specifically named or not), in language which would directly engage the public - for example, because it was highly persuasive or emotive. An example of such a case was Case AUTH/2404/5/11 where the Panel concluded that the content of a press release and briefing material for spokespersons would encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. The Panel particularly noted a statement in the press release which described Pradaxa as 'leading the way in new oral anticoagulants/direct thrombin inhibitors ... targeting a high unmet medical need'. Another example was Case AUTH/2147/7/08; in which the Panel considered that describing Gardasil as the 'world's leading four-type HPV vaccine' and stating that it provided 'unmatched cervical cancer protection' would encourage patients to ask for the medicine.

The present case, Case AUTH/2528/8/12, was not comparable to the cases cited above where the Panel ruled a breach of Clause 22.2 (second sub-paragraph) or its predecessor under the 2006 Code (Clause 20.2). As explained in detail in Shire's response to Genzyme's allegation of a breach of Clause 22.2, the press release presented newsworthy scientific data in measured and non-emotive language; indeed, it was very clear from the language of the press release that statements were not made for the purpose of encouraging members of the public to ask their health professional to prescribe VPRIV. Shire noted the different target audiences of the Pradaxa and Gardasil press releases on the one hand, and the VPRIV press release on the other. Articles based on the Pradaxa press release were published in the Daily Mail, The Telegraph and the Express, indicating that the press release had been very much directed at the lay person. This was similarly true of a Gardasil press release (Case AUTH/2147/7/08) which was disseminated to the consumer press, with a title specifically referring to school girls in the UK ('School girls in the UK will not benefit from the World's leading four type human papillomavirus (HPV) vaccine, Gardasil'). In contrast, whilst the press release now at issue was accessible to the public on Shire's global corporate website, it was directed to the investor and scientific communities. As explained in detail in Shire's response to Genzyme's complaint, patient organisations played an important role within the scientific community for the orphan Gaucher disease.

Finally, Shire noted for the sake of completeness that the Panel implied that because the press release was unbalanced, it was likely to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. However, this did not logically follow. Even if the press release was unbalanced (which Shire disputed), this did not necessarily mean that it was likely to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. Indeed, the Panel did not explain as to how it had reached this conclusion; namely, what it was in the non-promotional press release which would create such an effect on members of the public. The Panel's lack of reasoning in this respect was indicative of the arbitrary nature of its conclusion.

**RESPONSE FROM GENZYME**

Genzyme referred to its general comments made in response to Shire's appeal at Point 1 above.

Genzyme noted that Shire had contested the Panel ruling that the press release did not present information about VPRIV in a balanced manner. Genzyme alleged that Shire's arguments in this respect were directly contradicted by the fact that, as noted by the Panel and as further discussed in Genzyme's comments' at Point 1 above, the press release was misleading.

Genzyme noted Shire's submission that it had no intention in publishing the press release to encourage patients to ask their health professionals to prescribe VPRIV. According to Shire, in order to justifiably rule that a statement constituted a breach of Clause 22.2 of the Code, the Panel was required to demonstrate that such an intention existed. Genzyme submitted, however that the distribution of the press release to patient organisations, and indirectly to patients through the website of the Gauchers Association, and the inclusion of claims regarding the superiority of VPRIV vs Cerezyme summarised in the subheading, demonstrated Shire's intention to encourage patients to ask their health professionals to prescribe VPRIV.

Genzyme also noted Shire's claim that the press release did not have the effect of encouraging patients to ask their health professionals to prescribe VPRIV. This argument was based on an allegation that there was a contradiction between the Panel ruling that the press release was not promotional and the Panel's ruling that the press release was likely to encourage patients to ask their health professionals to prescribe VPRIV. Genzyme alleged that the press release was both promotional and likely to encourage patients to ask their health professionals to prescribe VPRIV. Genzyme's argument that the press release was promotional was supported by the definition of promotion found in Clause 1.2 of the Code, the previous rulings of the Panel and the case law of the Court of Justice of the European Union discussed above. Also as noted above, Genzyme did not challenge the objective exchange of scientific information through press releases. However, Shire's press release overstepped the appropriate boundaries of scientific exchange and made misleading and unfair comparative claims.

**APPEAL BOARD RULING**

The Appeal Board noted its rulings in the above and it considered that the press release at issue was misleading and likely to encourage members of the public to ask their health professional to prescribe VPRIV, a prescription only medicine. The Appeal Board upheld the Panel's ruling of a breach of Clause 22.2. Shire's appeal on this point was unsuccessful.

**5 The press release disparaged Cerezyme**

**COMPLAINT**

Genzyme alleged that the press release disparaged Cerezyme in breach of Clause 8.1. Genzyme noted that Shire asserted that the press release 'did not in anyway disparage Genzyme's product' and that 'The information in the press release was factual and further, was accurate, fair, balanced and could be substantiated'. Shire concluded that 'It cannot be concluded (as [Genzyme had] alleged) from the press release that Cerezyme was a relatively ineffective treatment of Gaucher disease'.

Genzyme alleged that the plain words of the press release and the ensuing misleading scientific analysis completely undercut Shire's position. The press release contained a comparative/superiority claim that was not included in the underlying poster. Moreover, the scientific analysis that served as the basis for this claim was flawed as detailed above.

**RESPONSE**

Shire contended that nothing in the press release disparaged Cerezyme.

Genzyme did not explain how the 'plain words of the press release' disparaged Cerezyme. To disparage a product meant to speak of it in a disrespectful or belittling way. In contrast, all references in the press release to Cerezyme were impartial, specifically:

- The statement directly under the headline highlighted the results achieved with VPRIV, without criticising Cerezyme explicitly or implicitly; and
- The difference in improvement from baseline was reported entirely objectively.

Accordingly, Shire submitted that an analysis of the plain words of the press release demonstrated exactly the opposite of what Genzyme alleged.

As explained in Shire's response to the allegations in Points 1, 2 and 3, the presentation of data in the press release was sound; Shire therefore strongly refuted Genzyme's allegation that the scientific analysis was flawed or misleading. The data presented for Cerezyme was consistent with data previously presented by Genzyme. It was undisputed that the patients in the Cerezyme cohort did not show a statistically significant improvement in BMD from baseline at nine months. The press release presented these results, but it did not purport to draw any conclusions based on them.

Further, the press release provided an appropriate degree of context so that the significance of the information might be evaluated by the reader. In particular, it was clear that BMD was evaluated as an exploratory endpoint, and further that femoral neck changes from baseline in both cohorts were non-significant at either 9 or 24 months. Accordingly, as during inter-company dialogue, it could not be concluded from the press release (as Genzyme had alleged) that Cerezyme was a relatively ineffective treatment for Gaucher disease.

In summary, the references to Cerezyme in the press release were not disparaging and were, in any event, accurate, balanced, fair and substantiated.

**PANEL RULING**

The Panel noted that Clause 8.1 required that the medicines, products and activities of other pharmaceutical companies must not be disparaged. The supplementary information to that clause further noted that much pharmaceutical advertising contained comparisons with other products and, by the nature of advertising, such comparisons were usually made to show an advantage of the advertised product over its comparator. Provided that such critical references to another company's

products were accurate, balanced, fair etc, and could be substantiated, they were acceptable under the Code. Unjustified knocking copy in which the products or activities of a competitor were unfairly denigrated was prohibited under this clause. Attention was drawn to the requirements for comparisons set out in Clauses 7.2 to 7.5.

Whilst the Panel noted its ruling above in relation to the misleading comparisons between VPRIV and Cerezyme, on balance the Panel did not consider that such comparisons amounted to disparagement as alleged. The claims, although ruled above to be misleading, were so in relation to positive comments about VPRIV. There was no implication that Cerezyme was not effective in increasing BMD in Gaucher disease. No breach of Clause 8.1 was ruled. This ruling was appealed by Genzyme.

**APPEAL BY GENZYME**

Genzyme referred to its general comments made in its appeal at Point 4 above.

- Clause 8.1

Clause 8.1 of the Code stated:

> 'The medicines, products and activities of other pharmaceutical companies must not be disparaged.'

The supplementary information stated:

> 'Much pharmaceutical advertising contains comparisons with other products and, by the nature of advertising, such comparisons are usually made to show an advantage of the advertised product over its comparator. Provided that such critical references to another company's products are accurate, balanced, fair, etc. and can be substantiated, they are acceptable under the Code.'

Genzyme noted that the Panel had considered that, overall, press release was not a fair reflection of the data and was misleading. The Panel also concluded that, the press release implied that the studies cited had produced robust confirmatory data that VPRIV significantly improved lumbar spine BMD and that Cerezyme did not and that this was not so. This clear implication of inefficacy of Cerezyme in the treatment of BMD, when it was actually effective, disparaged to Cerezyme in breach of Clause 8.1.

Genzyme noted that it had previously alleged that the press release contained misleading comparisons between VPRIV and its product, Cerezyme, and suggested that Cerezyme was less effective than had been shown by the evidence. Specifically, the subheading of the press release was 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months' (emphasis added). Paragraph five of the press release also described how the clinical study showed 'clinically and statistically significant improvement from baseline in mean [lumbar spine'] Z-score ... at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme' (emphasis added). Paragraph five of the release also presented, in direct proximity, data from patients treated with VPRIV and Cerezyme without revealing the substantial differences in baseline and how these differences might have limited the potential improvement of patients in the Cerezyme cohort.

Genzyme noted that although the Panel acknowledged in its ruling that the press release contained misleading comparisons, it did not consider that, on balance, such comparisons amounted to disparagement as alleged. The Panel further noted that there was no implication that Cerezyme was not effective in increasing BMD in Gaucher disease.

This conclusion directly contradicted the Panel's ruling that the press release breached Clauses 7.2 and 7.3 by including misleading comparisons and unfairly reflecting the study results by failing to fully explain the potential impact of the substantial differences in the baseline BMD measures in the two cohorts on the study results. More specifically, the Panel concluded that:

- 'The Panel disagreed with Shire's repeated assertions that no comparative or superiority claims were made';
- 'The Panel noted that despite the limitations of the data noted above, the title and subheading of the press release as set out above was unequivocal';
- 'The Panel did not accept Shire's submission that the press release made no comparative claims';
- 'The Panel was concerned that the press release was not clear that the extension study from which the BMD results were obtained was not a head-to-head study of VPIRV and Cerezyme; it gave the contrary impression in this regard. In addition, the Panel did not consider that it was sufficiently clear from the press release that BMD was a pre-specified exploratory endpoint';
- 'Exploratory endpoints could not be used as the basis for a robust comparison of medicines. The Panel considered that the press release was misleading in that regard and ruled a breach of Clause 7.2';
- 'The Panel considered that overall the press release was not a fair reflection of the data. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the findings';
- 'The Panel considered that Shire's assertions that the press release contained no direct comparisons between VPRIV and Cerezyme and that no confirmatory claims were stated or implied were disingenuous';
- 'Given the exploratory nature of the BMD analysis it was self evident that the studies were not powered to provide confirmatory findings on BMD. The press release gave a contrary impression';
- 'The Panel considered that the press release implied that the studies cited had produced robust confirmatory comparative data that VPRIV

significantly improved lumbar spine BMD and that Cerezyme did not. This was not so. The data was such that no conclusive comparisons could be made'; and
- 'The Panel had concerns about the content of the press release. It was not a fair reflection of the study'.

Genzyme alleged that in addition, the Panel had already ruled that the unbalanced and misleading presentation of clinical data in the context of a comparison of competitor products could be considered disparaging for one of the products and, thus, in breach of Clause 8.1. In Case AUTH/2231/5/09, the Panel ruled that the omission of certain elements in the presentation of clinical data was disparaging to one of the medicines being compared. In the current case, Case AUTH/2528/8/12, the Panel ruled that the press release gave the misleading impression that the clinical data presented was the result of a robust and head-to-head clinical comparison between VPRIV and Cerezyme and that this data demonstrated that VPRIV had an advantage over Cerezyme. Genzyme submitted that information that misled its intended audience regarding the advantages of VPRIV automatically misleadingly implied that Cerezyme had a disadvantage as compared with VPRIV. This was disparagement of Cerezyme in breach of Clause 8.1.

Given the Panel's conclusions, Genzyme was unsure how it could conclude anything other than the Shire press release contained misleading comparisons concerning Cerezyme that disparaged the product by improperly suggesting that it was less effective than VPRIV in improving BMD in patients with Gaucher disease than had been demonstrated by the evidence. The above arguments supported a ruling of a breach of Clause 8.1.

**RESPONSE FROM SHIRE**

Shire referred to its general comments made in response to Genzyme's appeal at Point 4 above.

In its appeal of the Panel's ruling of no breach of Clause 8.1, Shire noted that Genzyme had argued that it was logically inconsistent for the Panel to conclude that the press release had not disparaged Cerezyme given its conclusion that the press release misleadingly implied that confirmatory comparative conclusions could be drawn from exploratory findings (and ruled various breaches of Clauses 7.2 and 7.3). Genzyme's argument therefore depended on the assumption that material which contained misleading comparisons would, *de facto*, disparage a competitor's product. However, Shire submitted that this could not be the case otherwise material which was ruled to contain misleading comparisons (in breach of Clause 7.3) would automatically be ruled disparaging without the need for a separate assessment, which could not have been the intention behind the Code.

Shire noted that Genzyme had only quoted the first paragraph of the supplementary information to Clause 8.1, which stated that:

'Much pharmaceutical advertising contains comparisons with other products and, by the nature of advertising, such comparisons are usually made to show an advantage of the advertised product over its comparator. Provided that such critical references to another company's products are accurate, balanced, fair etc, and can be substantiated, they are acceptable under the Code.'

In quoting this extract, Genzyme sought to argue that material which was held not to be accurate, balanced, fair and substantiated must be disparaging. According to Genzyme's argument, as the Panel considered the press release to be unbalanced and unfair (and therefore misleading under Clauses 7.2 and 7.3), it must also be in breach of Clause 8.1. However, it was clear from the second paragraph of the supplementary information to Clause 8.1 that something else was required for material to be disparaging: 'Unjustified knocking copy in which the products or activities of a competitor are unfairly denigrated is prohibited under this clause'.

Shire submitted that the above wording reflected the essence of Clause 8.1 which prohibited material which unjustifiably knocked or unfairly denigrated the products/activities of a competitor. This was a different test than that applied to the concept of 'misleading' under Clauses 7.2 and 7.3. Not all negative or unfavourable statements about a competitor's products/activities would be disparaging. Rather, 'disparaged' implied an intentional, targeted and scornful attack ie 'to bring discredit or reproach upon'; 'to lower in position or dignity; to degrade'; 'to speak of or treat slightingly; to treat as something lower than it was; to undervalue; to vilify'. The word 'denigrate', used in the supplementary information, was similarly strong ie 'to blacken, sully, or stain (character or reputation); to blacken the reputation of (a person, etc.); to defame'. (The compact Edition of the Oxford English Dictionary).

Further, it was also clear from previous Panel rulings that, for the purposes of Clause 8.1, 'disparage' was given its natural meaning, as set out above. For example, in Case AUTH/2477/2/12 a breach of Clause 8.1 was ruled because the representative in question had misleadingly implied that there was no clinical reason to prescribe the competitor product. This conclusion was consistent with the meaning of disparage, because the product of the competitor was discredited. Further in Case AUTH/2475/1/12 the Panel ruled breach of Clause 8.1 (upheld on appeal) on the basis that the particular presentation of a table in a leavepiece implied that continuing to smoke was safer than trying to quit with varenicline (a product indicated for smoking cessation). This was clearly disparaging as it discredited the entire purpose of the product. As explained above, the natural meaning of 'disparage' also encompassed language which belittled a competitor's product. An example of material which was ruled to be disparaging in this sense was found in Case AUTH/2316/5/10 where a training slide contained the following wording about a competitor product: 'Abstral SmPC states 'The bioavailability of Abstral

***has not been studied*** but is ***estimated*** to be 70%' (how do they know – on what basis?)' [original emphasis]. The Panel considered that by adding bold emphasis to the wording quoted from the competitor's SPC, and by including the question 'how do they know – on what basis?', the slide presentation disparaged the competitor's product.

Accordingly, if the Panel's rulings of breaches of Clause 7.2 and 7.3 were upheld (which were contested by Shire in its own appeal), it did not follow that Shire had also disparaged Cerezyme. Indeed, Shire strongly disputed that it had done so. Specifically, Shire had not discredited or belittled Cerezyme. The exploratory data summarised in the press release were newsworthy in indicating a statistically significant improvement in BMD at 9 months in patients treated with VPRIV. The statements regarding Cerezyme were ancillary to this message and were included for the sake of accuracy and completeness. The Panel had recognised this in its ruling: 'There was no implication that Cerezyme was not effective in increasing BMD in Gaucher disease'.

Further, the entire tone of the press release was unemotive; it was not scornful or even critical of Cerezyme. It was also worth noting that, whilst Clause 8.1 did not appear to be limited to promotional communications, the supplementary information was clearly focussed on such communications:

> 'Much pharmaceutical advertising contains comparisons with other products and, by the nature of advertising, such comparisons are usually made to show an advantage of the advertised product over its comparator'; and
>
> 'Unjustified knocking copy [implicitly, advertising copy]...' (Emphasis added)

Shire submitted that this focus on promotional material might be a consequence of the fact that disparaging statements were more likely to be made in a promotional context, where the language was naturally stronger and intentionally persuasive. Shire noted again that, as it maintained the press release was ruled to be non-promotional.

Finally, Shire submitted that the case relied upon by Genzyme, Case AUTH/2231/5/09, did not support Genzyme's contention that the press release was disparaging of Cerezyme. In that case, the Panel concluded that the claim at stake ('There is some concern as to whether the superior efficacy achieved by Xarelto was at the cost of increased bleeding risk') would be read as a direct comparison of the two products, when in fact there was only indirect comparative data available. The Panel concluded that the medical information letter had not provided sufficient detail about the comparisons and was disparaging. However, contrary to what Genzyme suggested, the outcome of this case could not be interpreted to mean that, in all instances where the presentation of clinical data was held to be misleading, a ruling of Clause 8.1 should follow automatically. Indeed, it was necessary to analyse what, precisely, had been said about the competitor's product. In Case AUTH/2231/5/09, the tone of the language was negative about the competitor product ('***at the cost of*** increased bleeding risk'). In the present case, Shire contested the Panel's ruling that the press release was misleading but even if that ruling was upheld, Shire submitted that the language and message of the press release was not scornful, pejorative or in any way disparaging of Cerezyme. Therefore, in contrast with the cases where a breach of Clause 8.1 was ruled, the message of the press release was not critical of Cerezyme; rather, Shire was simply reporting the data gathered on the exploratory endpoint.

Accordingly, Shire submitted that the Panel's ruling of no breach of Clause 8.1 of the Code should be upheld.

**FINAL COMMENTS FROM GENZYME**

Genzyme referred to its general comments made at Point 4 above.

Genzyme noted that Shire had interpreted Genzyme's argument to be dependent on the assumption that material which contained misleading comparisons would *de facto*, disparage a competitor's product. This was not correct. The reason why the press release was disparaging was because the claims in the press release discredited, lowered in position and undervalued Genzyme's product.

The headline of the press release stated:

> 'In a head-to-head trial between VPRIV and Cerezyme (imiglucerase), only patients treated with VPRIV experienced statistically significant improvement in lumbar spine bone mineral density at 9 months.'

Genzyme alleged that this headline disparaged Cerezyme because it misleadingly implied that it was inferior and thus undervalued the medicine and lowered its position. In fact in Case AUTH/2475/1/12 to which Shire referred, Shire acknowledged that a breach of Clause 8.1 was ruled because the representative in question had misleadingly implied there was no clinical reason to prescribe the competitor product. Therefore it was possible to disparage a product by misleading implication.

Genzyme submitted that Shire's re-interpretation of Clause 8.1 and assertion that the phrase 'Unjustified knocking copy ...' was dominant in some way over the paragraph which Genzyme quoted was simply mistaken. Furthermore, whether it was mistaken or not, interpretation of the whole of this paragraph showed that the press release contravened Clause 8.1, for the following reasons:

> The subheading of the press release clearly claimed that only VPRIV, and not Cerezyme, produced statistically significant improvements in lumbar spine BMD, and therefore strongly

implied that Genzyme's product was ineffective in treating bone mineral density. In contrast the experience of many years use of Cerezyme in many patients had been published and clearly showed that it did improve BMD.

Further the press release went on to state 'Clinically and statistically significant improvement from baseline in mean LS Z-score was seen at nine months of treatment with VPRIV, but not in the cohort of patients treated with Cerezyme'. The press release clearly stated that no clinically or statistically significant improvement from baseline was made with Cerezyme. This was disparaging as it implied that there was no clinical reason to prescribe Cerezyme.

Genzyme alleged that finally Shire tried to distinguish Clause 7.2 completely from Clause 8.1 of the Code. However, the supplementary information to Clause 8.1 actually expressly linked the two clauses:-

'Attention was drawn to the requirements for comparisons set out in Clauses 7.2 to 7.5.'

This strongly reinforced the position that by failing to present data in an 'accurate, balanced, fair [and] objective' manner and distorting data, competitors' products could be disparaged.

**APPEAL BOARD RULING**

The Appeal Board noted the supplementary information to Clause 8.1 and its rulings in Points 1, 2 and 3 above. The press release made comparative claims that VPRIV had an advantage over Cerezyme in lumbar spine Z score. This advantage was based on exploratory data and in relation to comparing each patient group with its baseline rather than comparing between groups. To claim that VPRIV significantly improved lumbar spine BMD and Cerezyme did not, based on exploratory data, was misleading and inaccurate. The Appeal Board considered that, on balance, by making claims that were ruled to be misleading and inaccurate, Cerezyme had been disparaged and thus it ruled a breach of Clause 8.1. Genzyme's appeal on this point was successful.

**6 The press release had not been certified**

**COMPLAINT**

Genzyme considered that failure to certify the press release was in breach of Clauses 14.1 and 14.5. Genzyme noted that Clause 14 required promotional and other materials to be certified by two persons in the UK on behalf of the company prior to release in the UK. For promotional materials, the certification must state that the materials complied with relevant regulations and the Code was not inconsistent with the marketing authorization and the summary of product characteristics (SPC) and was a fair and truthful presentation of the facts about the medicine. Although the supplementary information to Clause 3 recognized that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited, it clearly stated that such exchange was only permitted 'provided that any such information or activity did not constitute promotion'.

During inter-company dialogue, Shire confirmed that the press release had not been certified and that as a piece of 'non-promotional material, it must only be 'reviewed' pursuant to Clause 14.3. Shire had repeatedly concluded that certification was unnecessary because the press release was not promotional given that it was only directed to investors, shareholders and relevant scientific media.

Genzyme considered that the press release was promotional both as a matter of law and fact. As a matter of law, the Court of Justice of the European Union and the Panel had both concluded that the mere fact that a communication was a press release did not exclude it from being promotional. Similarly, Clause 1.2 of the Code defined 'promotional' broadly to include any activity undertaken by a pharmaceutical company or with its authority which promoted the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines. Consequently, the threshold issues in determining if a communication was promotional were the nature of its distribution and whether it contained information regarding medicines which was intended or likely to influence, either directly or indirectly, the behaviour of patients, prescribers or purchasers. First, as a matter of fact, the press release was widely distributed in the UK through placement on the homepage of Shire's global website, distribution through its public relations agents to the patient group for Gaucher disease in the UK and publication by various UK and European newswires. It was not, as claimed by Shire, targeted only to corporate investors, shareholders and scientific media. Second, it was indisputable that the press release discussed VPRIV and Cerezyme. Third, and importantly, the press release did not qualify as 'legitimate scientific exchange' because it did not simply and objectively describe the study data or the related poster. In fact, the underlying poster made no comparative/superiority claims. In contrast, the press release made broad and unqualified superiority claims about the efficacy of VPRIV over Cerezyme and the effectiveness of VPRIV to treat Gaucher-related bone disease. For all of these reasons, Genzyme considered that the press release was promotional. As such, it must be certified before publication in the UK.

Given the volume and seriousness of the Code breaches, Genzyme strongly questioned whether the press release had been subjected to substantive or meaningful review as required by Clause 14.5. Genzyme considered that had Shire properly complied with its certification obligations, the press release would not have been issued. The above breaches constituted serious disregard of the letter and spirit of the Code.

**RESPONSE**

Shire contended that the press release was properly examined in accordance with the Code, and legitimately issued. Clause 14 provided that promotional material (Clause 14.1) and specific categories of non-promotional material (Clause 14.3) must be certified in advance. Where non-promotional information to the public (in accordance with Clause 22.2 of the Code) fell under one of the Clause 14.3 categories, the supplementary information to Clause 22.2 reiterated that the material in question must be certified in advance. However, whilst non-promotional press releases might fall within Clause 22.2 of the Code, they did not require advance certification, as specifically provided in the supplementary information to Clause 14.3:

> 'Other material issued by companies which relates to medicines but which is not intended as promotional material *per se*, such as corporate advertising, press releases, market research material, financial information to inform shareholders, the Stock Exchange and the like, and written responses from medical information departments or similar unsolicited enquires from the public etc, should be examined to ensure that it does not contravene the Code or the relevant statutory requirements' (emphasis added).

Shire maintained its position that the press release was non-promotional and therefore did not require certification under Clauses 14.1 and 14.5; and the press release did not fall within any of the specific categories of non-promotional material set out in Clause 14.3 (which required certification) and was appropriately examined in accordance with the supplementary information to Clause 14.3 (applicable to 'Other Material') to ensure that it did not contravene the Code or the relevant statutory requirements.

Shire noted that Clause 1.2 defined the term 'promotion' as:

> '... any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines.'

Whether or not a communication constituted promotion depended on all the circumstances, including the nature of the communication and its intended audience, as well as its content and presentation (specifically, whether it contained information which was intended or was likely to influence the behaviour of health professionals or patients).

Shire submitted that a press release was not, *per se*, a promotional communication. In fact, in accordance with the company's clear internal guidelines on the issue and review of press releases (explained in detail below), Shire did not use press releases for promotional messages.

Shire stated that the fact that press releases 'could be considered promotional', as stated by Genzyme, did not mean that they were necessarily or invariably promotional in nature. Indeed, material must be assessed in light of its particular factual context. Genzyme cited two PMCPA cases where press releases were considered to be promotional, and where breaches of the Code were ruled. However, these rulings had no bearing on the case at stake. In Case AUTH/2355/9/10, the Appeal Board upheld the Panel's ruling and was of the view that:

- the press release made 'strong claims' for the product (for example, 'potential to save an additional eight lives each year');
- the language was 'highly emotive' (the product was entitled 'NICE says no to life saving treatment for childhood bone cancer' and the company stated that it wanted to ensure that young patients were 'provided with a fighting chance'; and
- the press release lacked balance.

Shire submitted that this was not comparable to the present case, where the information was presented in an objective and balanced way.

The other case referred to by Genzyme, Case AUTH/2201/1/09, did not support its allegations either. In that case, the Panel considered that the study results had been exaggerated in the title of the press release ('Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery'). Overall, the Panel considered that the press release in question was misleading and raised unfounded hopes of successful treatment, such that patients would be encouraged to ask for a specific prescription only medicine. However, those conclusions were specific to that press release and were not relevant in the present case where the information provided was factual, accurate and presented in an objective and balanced way.

Shire submitted that whilst Genzyme provided examples of press releases which were found to be promotional, it was also possible to provide examples of press releases which were found to be non-promotional in nature. For example, in Cases AUTH/2160/8/08 and AUTH/2161/8/08, a press release published on an area of a company's website marked for the media did not promote the medicine in question. Another example was Case AUTH/2464/12/11, where no breach of the Code was ruled in relation to a press release (which was considered to be non-promotional). In its ruling, the Panel commented on the supplementary information to Clause 14.3, which stipulated that non-promotional material (including press releases) should be examined to ensure that there was no contravention of the Code.

Shire stated that the press release was distributed via its agent. The intended audience was the investor community (potential and current), as well as relevant scientific and medical media. This was

consistent with all Shire press releases, which were sent either to the corporate community only, or to the scientific community only, or to both. Whilst the press release was not a price sensitive mandatory announcement, Shire considered the data to be newsworthy and of interest to the investor and scientific communities because treatment of the skeletal manifestations of Gaucher disease was an ongoing clinical concern. Had Shire not considered the data to be newsworthy then, under its own internal procedures, it would not have issued a press release.

Shire submitted that it was standard practice within the industry to publish press releases (such as the one at issue), reporting on new data, even when the information was not share price sensitive. Further, it was standard to publish such information on the global company website. The press release at issue was published on the homepage of Shire's global website; it was not published on the company's UK website because it was not directed to a specifically UK audience. It was placed on Shire's global website because it was a global press release of general media interest. Contrary to Genzyme's assertion that the press release was subsequently 'moved' to the 'Media' and 'Investor' tabs of Shire's global website, the press release was in fact posted and maintained on these sections but no longer appeared on the homepage because subsequent press releases were posted. In this context, Shire noted that the Panel had ruled that it was acceptable to have press releases in a 'media section' of a company website (Cases AUTH/2160/8/08 and AUTH/2161/8/08).

Shire noted Genzyme's allegation that it had acted recklessly in providing the press release to a newswire, but submitted that it was important to clarify that this was the general corporate newswire and the standard communication channel for any press release of relevance to investors. Media organisations subscribed to the newswire and as such it was a 'pull' service. Further, Genzyme's statement that Shire (or its agent) provided the press release to another newswire, was incorrect. Shire knew that this newswire had a publishing side that editorialised news distributed via other wires, and that the pharmaceuticals sector was one that this newswire monitored and reported on. Accordingly, Shire suspected that it picked up the news from another source.

Shire submitted that patient organisations were an important part of the scientific community for Gaucher disease. Indeed, the Gauchers Association has a prominent role in the scientific community for Gaucher disease, including participation in peer reviewed scientific communications in Gaucher disease. Further, this year, the European Gaucher Alliance was a 'partner organisation' of the European Working Group on Gaucher disease ('EWGGD'), an independent group that brought together experts, patient organisations and researchers. The Gauchers Association presented in the scientific sessions at the 2012 EWGGD meeting in Paris and representatives from the Gauchers Association attending the event would have seen Shire's poster which was evaluated and accepted by the EWGGD's Scientific Committee.

Shire stated that the unique role of patient organisations in rare diseases in the scientific community was described on the European Gaucher Alliance Website:

> 'On an international level, because there are only a relatively small number of clinicians and scientists in the field and due to the initiative to involve patients in scientific and medical meetings, patients' support group leaders have developed personal relationships with doctors and scientists from around the world and have, through their professional approach, earned their respect and confidence. This has enabled individual patients' support groups to play an active role in enhancing collaboration between medical centres and individual patient groups in countries where this approach is still novel.'

Shire submitted that, as such, in this orphan disease area, patient organisations represented an integral part of the scientific community and it was appropriate to include their media arm in the distribution of a relevant, non-promotional press release.

The press release in question was provided to the Gauchers Association as it contained important information about the improvement in Gaucher-related bone disease in patients treated with VPRIV. It was very clearly sent to the UK Gauchers Association for information purposes only, under the cover of the following message (via Shire's agents):

> 'I hope this e-mail finds you very well.
>
> We wanted to share the latest Shire press release on VPRIV, which covers new VPRIV data being presented at the EWGGD today.'

Shire submitted that it was not its intention, and it was satisfied that its agents did not request any action from patient organisations in relation to press releases (for example, transmission of the information to patients). Providing the press release to the Gauchers Association did not render it promotional. The supplementary information to Clause 22.1 specifically provided for the supply of proactive information to the public (including patient organisations). Neither Shire nor its agents dictated what information should be provided to patients. In fact, the Gauchers Association did not post the press release when it was sent to them on 28 June 2012. The body of the press release was posted on the Gauchers Association website on 6 August 2012 and as Genzyme noted, The Gauchers Association added its introduction. These circumstances emphasised that Shire did not influence the way in which the Gauchers Association reported the information (or indeed whether it reported it at all).

Shire considered that Genzyme's suggestion that it should have marked the press release with the words 'for business only, not intended for the public' was nonsensical as 'the public' was a very broad term within the Code and included journalists and shareholders, as well as patients and patient organisations.

Shire submitted that the presentation of the data in the press release would not encourage health professionals to prescribe VPRIV; indeed, owing to its nature and distribution, a press release was not the normal channel of communication with health professionals. Further, the press release was not made for the purpose of encouraging members of the public to ask their doctor to prescribe the product. Rather, the press release represented the legitimate and genuine dissemination of scientific information.

Shire considered that the information was reported in the press release objectively and in a balanced manner. The clinical relevance of BMD in Gaucher patients was presented clearly and unambiguously:

> 'In Gaucher disease patients, BMD is generally reduced compared to individuals without Gaucher disease, often resulting in lower Z-scores. Measuring BMD can help to quantify the impact of Gaucher disease on the patient's bone and can help identify the potential benefits of treatment in improving Gaucher-related bone disease.'

It is also clearly stated that BMD was evaluated as an exploratory endpoint, underlining the fact that the press release did not draw confirmatory conclusions.

Shire stated that, further, whilst Genzyme argued that the titles of the published articles reporting on the press release underscored its misleading nature, it was necessary to consider the press release in its own right. A complaint could be judged only on the information provided by the pharmaceutical company or its agent to the journalist; not on the content of the article itself (Shire referred, by way of example, to Cases AUTH/2403/5/11 and AUTH/2404/5/11). The fact that certain journalists had independently created and subsequently used 'catchy' titles did not mean that the press release misled them or that it was promotional in nature. In any event, if Genzyme's argument was that certain journalists had drawn comparisons between VPRIV and Cerezyme (ie with their own independently created titles), then it should also be noted that other journalists did not do so, eg 'Shire presents additional Phase III VPRIV data' (BioCentury, 28 June 2012); 'Shire's VPRIV Shows Improvement in Gaucher-Related Bone Disease' (FlyOnTheWall, 28 June 2012); and 'Shire's VPRIV shows significant improvement in Gaucher-related bone disease' (CenterWatch, 29 June 2012).

Shire submitted that the press release was appropriately examined in accordance with the supplementary information to Clause 14.3 to ensure that it did not contravene the Code or the relevant statutory requirements. The press release did not fall within any of the specific categories of non-promotional material set out in Clause 14.3 (which required certification in a manner similar to that provided in Clause 14.1). The press release was, however, appropriately examined in accordance with the supplementary information to Clause 14.3 (applicable to 'Other Material') to ensure that it did not contravene the Code or the relevant statutory requirements.

Shire stated that it had robust procedures in place for assessing when information should be communicated in a press release, as well as for the preparation, review and dissemination of press releases (a copy of the slide set setting out the process, Corporate Press Releases: Guidance & Review Process, was provided). The press release at issue was reviewed in accordance with Shire's procedures, one of the aims of which was to ensure compliance with EU Codes, the UK Code being one of the strictest EU Codes.

Firstly, Shire used press releases as a vehicle of communication only when information was genuinely 'newsworthy'. This included newsworthy data generated by data analysis [slide 3] and significant data releases at scientific meetings [slide 6], but excluded (for example) the repetition of information already in the public domain (because such repetition was likely to be construed as promotional). Further, as a general principle, Shire considered press releases to be an appropriate vehicle when the audience included investors [slide 7]. In the present case, the data were considered to be newsworthy; the dissemination of the press release coincided with the EWGGD meeting where the same findings were reported for the first time in a poster presentation.

Secondly, Shire submitted that in preparing a press release, it abided by certain guiding principles, including to:

- Be accurate, balanced, fair and complete;
- Use a tone which was neutral or factual, not promotional or misleading; and
- Be concise and stick to the facts [slide 10]

These guiding principles were reflected in the content and tone of the press release at issue, as explained throughout this response.
Thirdly, Shire recognised the importance of reviewing press releases. In the case of a global press release (such as the one at issue), the review team included firstly: medical, legal and regulatory members of the product franchise team, and secondly: senior members from regulatory affairs, medical and legal.

The aims of the review process [slide 12] included the objectives of:

- Providing guidance regarding which information was worthy of a press release;
- Ensuring that a robust and efficient process existed for the preparation, review, and approval of press releases;
- Preventing, detecting and correcting potential breaches of FDCA, EU codes and other applicable laws (emphasis added).

Shire submitted that it was therefore important to note that the press release was reviewed for compliance with the EU Code, the UK Code being one of the strictest.

Further, Shire submitted that its procedure [slide 11] highlighted, *inter alia*, that the promotion of prescription products to the public was a criminal

offence outside the US and further that the pre-approval promotion of pharmaceutical products was a breach of law. The procedure set out specific Code guidance [slide 29] as follows:

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

Overall, Shire considered that its guidance demonstrated that the company drew a clear distinction between press releases and promotional communication. The company had robust procedures in place for ensuring that press releases did not become advertisements. Neither Shire nor its agents sought to influence the placement or content of any article ensuing from a press release.

**PANEL RULING**

The Panel noted that Clause 14.1 required that promotional material must not be issued unless its final form, to which no subsequent amendments would be made, had been certified by two persons on behalf of the company. Clause 14.1 also stated that materials listed in Clause 14.3 should be certified. Clause 14.5 required that the certificate for promotional material must certify that the signatories had examined the final form of the material and that in their belief it was in accordance with the requirements of the relevant regulations relating to advertising and the Code, was not inconsistent with the marketing authorization and the SPC and was a fair and truthful presentation of the facts about the medicine.

The Panel further noted that Clause 14.3 required certain non-promotional material be certified. The material listed did not mention press releases; however, it did include 'material relating to working with patient organisations'. The Panel considered that this Clause thus required that material sent proactively by a company to a patient organisation, including, *inter alia*, press releases, should be certified. The Panel considered that the provision of the press release to the patient organisation triggered the certification requirements and ruled a breach of Clause 14.1 and consequently Clause 14.5. These rulings were appealed by Shire.

**APPEAL BY SHIRE**

Shire referred to its general comments made its appeal at Point 1.

Shire submitted that the Panel's rulings of breaches of Clauses 14.1 and 14.5 followed from its conclusion that the press release fell within one of the Clause 14.3 categories of non-promotional information for which certification was mandatory, ie 'material relating to working with patient organisations as described in Clause 23 and its supplementary information' (Clause 14.3, second bullet). However, this conclusion depended on the premise that a press release sent proactively by a company to a patient organisation constituted material relating to working with patient organisations as described in Clause 23 of the Code. Shire strongly contested this premise.

Shire submitted that it was telling that the Panel did not quote the second bullet of Clause 14.3 in its entirety. Contrary to what the Panel suggested, this provision did not capture any and all material to which a patient organisation was exposed to; rather, it specifically captured the type of material described in Clause 23 and its supplementary information.

Shire submitted that on the plain wording of Clause 14.3 (second bullet), it was apparent that the kind of material for which certification was mandatory was that which related to '<u>working with</u> patient organisations' (emphasis added). Notably, therefore, the Code did not stipulate that all material provided to patient organisations was certified; if that was the intention then the Code would clearly state as such. Rather, certification was mandatory where there was a specific relationship between the pharmaceutical company and the patient organisation in relation to the activity in question.

Shire submitted that this interpretation was supported by the clear language of Clause 23, to which Clause 14.3 (second bullet) specifically referred. Indeed, Clause 23 was entitled 'Relationships with Patient Organisations' and covered interactions between the industry and patient organisations. Such interactions included the provision of funding (Clauses 23.4, 23.7) and the engagement of patient organisations to provide services (such as participation at advisory board meetings) (Clause 23.8). In summary therefore, Clause 23 covered situations where there was a two-way relationship between a pharmaceutical company and a patient organisation. As regards materials relating to working with patient organisations, Clause 23.3 specifically provided that:

> 'Companies working with patient organisations must have in place a written agreement setting out exactly what has been agreed, including funding, in relation to every significant activity or ongoing relationship.'

Further, the supplementary information to Clause 23.3 set out what such a written agreement must include and stated: 'Attention is drawn to the certification requirements as set out in Clause 14.3'.

Shire submitted that it was therefore very clear that the kind of written material falling within Clause 14.3

and requiring certification was, specifically, that which:

- documented an arrangement between a pharmaceutical company and a patient organisation
- was produced as a consequence of such arrangement/relationship (for example, sponsorship material prepared in accordance with the terms of an agreement between the company and patient organisation).

Shire submitted that this interpretation was consistent with the wording of Clauses 14.3 and 23. Conversely, the Panel's interpretation that a press release should be certified merely because it was sent to a patient organisation (amongst others) was inconsistent with the plain wording of Clauses 14.3 and 23.

Shire submitted that further, on a schematic interpretation of the Code, it was very clear that non-promotional press releases were not intended to fall within the categories of information which should be certified. Shire emphasised once again that press releases were specifically carved out of the Clause 14.3 categories of non-promotional information which required certification. In this regard, Shire noted the supplementary information to Clause 14.3, 'Examination of Other Material'.

Shire submitted that if there was a different rule for press releases sent to patient organisations, then the Code would surely state as such; however, it did not do so. Shire therefore complied with its obligation under the Code as the press release was appropriately examined in accordance with Shire's robust internal procedures detailed in its response to the complaint.

Shire submitted that finally, it was not inconsistent with the spirit of the Code that in terms of the certification there should be a distinction between material relating to working with patient organisations on the one hand, and non-promotional press releases sent to patient organisations (amongst others) on the other. An analogous distinction applied, for example, between educational material for the public relating to diseases/medicines (which must be certified in accordance with Clause 14.3, first bullet), and non-promotional press releases sent to the public and containing scientific/factual information not intended to be educational *per se* (no certification requirement). The different certification requirements for patient organisation material or educational material on the one hand and a press release sent to a patient organisation or the public at large on the other was justified. Material relating to working with patient organisations and educational material were analogous in having a very specific objective and finite target audience. As a consequence, the compliance requirements were more detailed and it was therefore logical that such material should be formally certified to confirm compliance with the Code. A press release, on the other hand, would often have a wider audience and a more general objective of conveying newsworthy information to interested parties. It would be entirely disproportionate to require formal certification under Clauses 14.1/14.5.

In summary, Shire submitted that there was a clear and justifiable distinction to be drawn between engaging in a two-way relationship with a patient organisation and independently despatching a press release to a patient organisation outside the context of any arrangement and with no instructions as to what is to be done with it. In the former case, materials documenting the relationship or pertaining to it must be certified in accordance with Clause 14.3; in the latter case, Shire submitted that there was no such requirement.

**RESPONSE FROM GENZYME**

Genzyme referred to its general comments made in its response to Shire's appeal at Point 1 above.

Genzyme noted that Shire claimed that there was no requirement for mandatory certification of the press release. According to Shire, provision of the press release to a patient organisation fell outside the scope of work with patient organisations covered by Clause 23 of the Code and its supplementary information.

Genzyme agreed that Clause 23 of the Code covered interactions with patient organisations but neither the clause nor its supplementary information provided an exhaustive list of interactions with patient organisations. The supplementary information to Clause 23 provided only a non-exhaustive list of examples of such interactions, and the provision of press releases to patient organisations was not explicitly excluded from this list. Accordingly, the claim that the provision of the press release fell outside the scope of working with a patient organisation was not supported by the language of either Clause 23 or its supplementary information.

Genzyme alleged that the press release was promotional and this position was supported by arguments made in its appeal. The requirement for mandatory certification of promotional materials provided for in Clause 14.1 thus applied to the press release.

**APPEAL BOARD RULING**

The Appeal Board noted its rulings above regarding Clause 22. The Appeal Board noted that press releases should not promote medicines. However as a consequence of its ruling of a breach of Clause 22.1 the press release needed to be certified irrespective of whether it was provided to a patient organisation. The Appeal Board upheld the Panel's rulings of breaches of Clauses 14.1 and 14.5. Shire's appeal on this point was unsuccessful.

**7 Lack of prescribing information**

**COMPLAINT**

Genzyme noted that Clause 4.1 required that 'the prescribing information listed in Clause 4.2 must be provided in a clear and legible manner in all promotional material for a medicine ....'. The prescribing information must include, but was not limited to, a concise statement of common side-effects, serious side-effects, precautions and contra-indications, as well as a short statement of information in the SPC relating to the dosage and method of use relevant to the indication(s) quoted in the advertisement.

Shire asserted that as the press release was non-promotional in nature, there was no real need to provide prescribing information.

Genzyme alleged that yet again, Shire had inappropriately attempted to circumvent the requirements of the Code by conveniently concluding that the press release was not promotional. Genzyme considered that the press release was promotional and made superiority claims that went well beyond the underlying poster. Furthermore, the press release did not contain the UK prescribing information required by Clause 4.1 nor did such information otherwise accompany the wide distribution of the press release. Such conduct breached Clause 4 of the Code. Genzyme did not consider that the assertion that the press release was not promotional was a defence to these clear breaches.

**RESPONSE**

Shire noted that whilst Clause 4.1 required that the prescribing information must be included in all promotional material for a medicine, this did not apply for non-promotional material. Indeed, the advice on the PMCPA website (dated 17 May 2012) specifically stated that:

> 'Press releases about a medicine do not require prescribing information, although it is considered good practice to include a summary of product characteristics.'

Further, the supplementary information to Clause 22.2 of the Code stated that:

> 'It is good practice to include the summary of product characteristics with a press release or press pack relating to a medicine.'

Shire stated that, consistent with the guidance of the PMCPA, its practice was to include the summary of product characteristics with any press release (as reflected in its internal guidance for press releases, slide 29]); and it instructed its agents to do likewise. Shire confirmed that the summary of product characteristics was provided with the press release by Shire's agent (with the exception of the dissemination to a newswire, due to the practical considerations).

Shire submitted that the allegation that it inappropriately attempted to circumvent the requirements of the Code by conveniently concluding that the press release was not promotional was without foundation. Indeed, Genzyme's reasoning was comprehensively circular: on the basis that the press release was non-promotional (as Shire submitted), there was no requirement to include the abbreviated prescribing information; thus there was no circumvention of the requirements of the Code. In fact, had the press release included the abbreviated prescribing information, it might have given a misleading message to the prescribers and the public, namely that the material was promotional in nature and designed to encourage members of the public to ask their doctor to prescribe a specific prescription only medicine. Instead, for the sake of completeness, the press release simply referred to the fact that the prescribing information might differ between countries, and that the US prescribing information might be accessed via Shire's website. This was consistent with the fact that the press release was a global press release and that this was a requirement of Shire's Corporate Press Release Guidance and Review Process [slide 20].

**PANEL RULING**

The Panel noted that Clause 4.1 required prescribing information to be provided in a clear and legible manner in all promotional material for a medicine except for abbreviated advertisements. The Panel noted its ruling at Point 6 above that the press release was not promotional and considered that thus it did not require prescribing information. No breach of Clause 4.1 was ruled. This ruling was appealed by Genzyme.

**APPEAL BY GENZYME**

Genzyme referred to its general comments regarding Clause 4.1 made in its appeal at Point 4 above.

- Clause 4.1

Genzyme alleged in its complaint that the press release was in breach of Clause 4.1 which stated that, 'The prescribing information listed in Clause 4.2 [the UK prescribing information] must be provided in a clear and legible manner in all promotional material for a medicine....'. Specifically, Genzyme argued that the press release was promotional as both a matter of law and of fact. This position was based on previous Panel rulings (Cases AUTH/2355/9/10 and AUTH/2201/1/09) and the case law of the Court of Justice of the European Union (Damgaard) establishing the principle that press releases could be promotional. Clause 1.2 of the Code broadly defined promotion to include:

> '... any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines.'

Genzyme agreed that the threshold issues in determining whether a communication was promotional were its content and the nature of its distribution.

Genzyme submitted that in concluding that the Shire press release was not promotional the Panel appeared to have misunderstood Genzyme's argument on this issue. The Panel noted that:

> '... Genzyme's allegation that the press release was promotional appeared to be based on the fact that a press release which contained information about a prescription only medicine was distributed to a patient organization. On this narrow point, and given its comments above, the Panel did not consider that the press release was promotional ....'

The audience to whom a press release was distributed was only one of the factors that should be considered in determining whether the press release was promotional. Genzyme acknowledged that the fact that a press release was addressed to a patient organization did not, of itself, lead to an automatic conclusion that the release must be considered promotional.

Genzyme did not believe, and had never intentionally argued, that the distribution of the press release to a UK patient organisation was the key or only argument to support the position that the press release was promotional. However, in light of Genzyme's arguments and previous opinions by the Panel concerning the content of the press release, there were strong arguments to support a conclusion that the press release was promotional.

Although Genzyme agreed with the Panel's ruling that press releases were not *per se* promotional, it alleged that, as articulated in the Code and as conceded by Shire, the facts and circumstances of each communication should determine its treatment under the Code. In this case, the press release went beyond the simple, objective recitation of study results. Both its content and distribution mechanism were promotional.

- The promotional nature of the contents of the press release

Genzyme alleged that the press release extended beyond an objective recitation of the study results and made broad and unqualified product and superiority claims. The press release made such broad and unqualified claims about the superiority of VPRIV over Cerezyme and the effectiveness of VPRIV in treating bone mineral density in patients with Gaucher disease. This was acknowledged in the ruling. The Panel also acknowledged that the press release presented clinical data in a misleading and unbalanced manner. Moreover, the Panel acknowledged that the press release:

> '... was likely to encourage members of the public to ask their health professional to prescribe a specific prescription only medicine....'

Genzyme submitted that all of the above elements demonstrated that Shire intended to present VPRIV in a more positive light than Cerezyme and influence patients in their decision to ask their health professionals to prescribe VPRIV instead of Cerezyme.

Genzyme submitted that despite acknowledging that the press release was likely to encourage patients to ask their treating physician to prescribe VPRIV, a fundamental criterion in determining whether material aimed at patients was intended to be promotional, the Panel ruled that the press release was not promotional. This conclusion appeared illogical and could, be justifiably challenged on the basis of the provisions of Clause 1.2 of the Code, the case law of the Court of Justice of the European Union, and previous Panel rulings.

Genzyme stated that, in its view, the only logical consequence of the Panel's ruling that Shire's press release was likely to encourage members of the general public to ask their health professional to prescribe VPRIV was that the press release fell within the scope of promotion as defined in Clause 1.2. That the press release contained comparative and superiority claims concerning VPRIV based on a misleading and unbalanced presentation of the available clinical data could only further support this conclusion. The conclusion was also supported by the previous rulings of the Panel and the case law of the Court of Justice of the European Union.

Genzyme noted that in its complaint it cited Cases, AUTH/2355/9/10 and AUTH/2201/1/09 in support of the proposition that a press release could be promotional based upon its content. Genzyme also cited the ruling of the Court of Justice of the European Union (Damgaard). In that case, the Court concluded that any information regarding the properties or availability of a medicine which was intended or likely to influence, either directly or indirectly, the behaviour of patients or members of the public constituted promotion of that medicine. A press release containing such information about a prescription only medicine could constitute prohibited promotion of a prescription only medicine to the public.

- The manner in which the press release was distributed

Genzyme alleged that the press release was distributed widely in the UK through placement on the homepage of Shire's global website, distribution through its public relations agents to the largest patient group for Gaucher disease in the UK, and publication by various UK and European newswires. This demonstrated that the press release was not targeted only to corporate investors, shareholders, and scientific media as initially submitted by Shire. In combination with the promotional content of the press release, the distribution of the press release to a wider audience constituted promotional activity.

Genzyme alleged that, in light of its arguments above and of the Panel's opinions about the content of the release, there were strong arguments to

support a conclusion that the press release was promotional. This conclusion was also supported by Clause 1.2 which defined promotion as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines;' by previous rulings of the Panel, and by related case law of the Court of Justice of the European Union. Further, as noted in the Panel's ruling, Shire conceded that it did not include the prescribing information with the press release when it was distributed in the UK. All of the above supported a ruling of a breach of Clause 4.1.

**RESPONSE FROM SHIRE**

Shire referred to its general comments made in its response to Genzyme's appeal at Point 4 above.

Shire reiterated that prescribing information was not required as the press release was not promotional. To have included prescribing information would have misled as to the nature of the press release as it would have wrongly implied a promotional purpose.

Shire maintained that the previous cases did not support Genzyme's claim that the press release was promotional. In these circumstances, and for all the reasons explained above and Shire's original response, it must be concluded that the press release was non-promotional. Accordingly, the Panel's ruling of no breach of Clause 4.1 should be upheld.

**FINAL COMMENTS FROM GENZYME**

Genzyme referred to its general comments about promotion made at Point 4 above.

**APPEAL BOARD RULING**

The Appeal Board noted its ruling above of a breach of Clause 22.1 at Point 4. The Appeal Board considered that the inclusion of prescribing information would not make the item at issue acceptable. Press releases should not promote medicines. However, as consequence of its ruling of a breach of Clauses 22.1, the item was promotional and thus the Appeal Board ruled a breach of Clause 4.1. The appeal on this point was successful.

**8 Disparaging and unsubstantiated comparisons with Cerezyme brought discredit on to the pharmaceutical industry**

**COMPLAINT**

Genzyme alleged that Shire's numerous breaches of the Code were so serious as to bring discredit upon, and reduce confidence in, the pharmaceutical industry.

**RESPONSE**

Shire disputed Genzyme's allegations in full, including its allegations that the press release:

- was promotional in nature;
- contained disparaging or unsubstantiated comparisons; or
- was distributed with 'reckless neglect' (Shire referred to the sound procedures that it had in place to ensure a proper and thorough review of all press releases and the responsible manner in which it controlled the activities of its agents).

Consequently, Shire strongly refuted Genzyme's allegation that it had reduced confidence in or brought discredit upon the pharmaceutical industry in breach of Clause 2, which was reserved as a sign of particular censure. The main focus of Shire's resources had been and continued to be on meeting the continuing demand for VPRIV in the UK, as well as in the other 39 countries where it had been approved since March 2010. Where appropriate, Shire had disseminated genuine scientific findings to the appropriate audience; this was a far cry from the campaign of 'reckless neglect' that Genzyme portrayed. It was regrettable that Genzyme was had made such accusations, which were without any foundation.

Genzyme noted that Shire did not address this allegation in inter-company dialogue; Shire contended that it strongly disputed all of Genzyme's allegations in inter-company dialogue. For the avoidance of doubt, it was Shire's position that there was no breach of Clause 2 either.

**PANEL RULING**

The Panel had concerns about the content of the press release. It was not a fair reflection of the study. The Panel noted its comments and rulings above at Points 1-7. The Panel noted that Clause 2 was a sign of particular censure and reserved for such use. The Panel considered that when assessing the acceptability or otherwise of claims in a press release companies should be mindful of the intended audience. Companies should be cautious when material was aimed at the consumer press or provided to a patient organisation. The Panel noted its comments and rulings about the press release at Points 1 to 7 above. The Panel considered that the implication that exploratory findings were of statistical and clinical significance in a press release directed at, *inter alia*, a patient organisation was wholly unacceptable and brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed by Shire.

**APPEAL BY SHIRE**

Shire referred to its general comments made in its appeal at Point 1 above.

Shire strongly refuted the Panel's ruling that it had brought discredit upon and reduced confidence in the pharmaceutical industry. Shire submitted that considering the severity of the Clause 2 ruling, the Panel's reasoning was regrettably sparse. However, whilst the Panel referred to its comments and rulings at Points 1 to 7, it appeared that its ruling was based particularly on its conclusions in relation to Clauses 7.2 and 7.3, namely that, in the Panel's view, the press

release misleadingly implied that confirmatory comparative conclusions could be drawn from exploratory findings. Further, it appeared that the Panel considered the severity of these breaches was exacerbated by sending the press release to a patient organisation. Accordingly, if the rulings of breaches of Clauses 7.2 or 7.3 were overturned, the Clause 2 ruling automatically fell away.

However, even if the Panel's ruling for breaches of Clauses 7.2 or 7.3 were not overturned (or indeed Clauses 14.1, 14.5 or 22.2), Shire submitted that this Clause 2 ruling was not warranted in this case.

As the Panel consistently noted in its rulings, a ruling of a breach of Clause 2 was intended as a sign of particular censure, and reserved for such use. The supplementary information to Clause 2 provided examples of activities that were likely to be in breach of Clause 2:

> '… prejudicing patient safety and/or public health, excessive hospitality, inducements to prescribe, inadequate action leading to a breach of undertaking, promotion prior to the grant of a marketing authorisation, conduct of company employees/agents that falls short of competent care and multiple/cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.'

Shire acknowledged that this was not an exhaustive list of the activities which might fall within the scope of Clause 2. However, it was essential that the parameters within which the industry operated were sufficiently certain. The industry should be entitled to trust, therefore, that in ruling on Clause 2 breaches, the Panel would take an approach which was consistent with its own guidance and with previous rulings. Any other approach would represent a violation of the principle of legal certainty. This was a particularly serious matter in the context of a Clause 2 breach considering the additional sanctions imposed, such a breach attracted, the most significant being damage to reputation as a consequence of the stigma attached to the ruling.

In the present case, Case AUTH/2528/8/12, however, the Panel had ruled a breach of Clause 2 in circumstances which did not fall within the above-listed examples, and which were not analogous to the above-listed examples. In particular, it was noted that the Panel had not alleged that the press release would prejudice patient safety and/or public health.

Further, Shire submitted that the Panel's ruling of a breach of Clause 2 was inconsistent with its approach in Case AUTH/2404/5/11 (also referenced above in the context of Clause 22.2 argument). It was important to note that this was a case which was specifically included as one of the Clause 2 'example cases' on the PMCPA's interactive web-version of the Code. In that case, a breach of Clause 2 was ruled, but in very different circumstances to those at stake here. Specifically, the press release was held to constitute promotion to the public (a breach of Clause 22.1 was ruled) and, additionally, the product was held to be promoted for an unlicensed indication (a breach of Clause 3.2 was ruled). The Panel specifically noted that promotion prior to the grant of a marketing authorisation was listed as an example of an activity that was likely to be in breach of Clause 2. Similarly, Case AUTH/2402/4/11 included as one of the Clause 2 'example cases' on the PMCPA's website, concerned promotional tweets which had not been certified. Breaches of Clauses 9.1, 22.1 and 22.2 were also ruled. The present case, Case AUTH/2528/8/12, was very different from these examples because, whilst a breach of Clause 22.2 was ruled, the press release was held to be non-promotional.

Shire submitted that further, even in cases where the material in question had been ruled to be promotional, a Clause 2 ruling was not automatic, and was still reserved as a sign of particular censure. For example, in Case AUTH/2355/9/10 the Appeal Board overturned the Panel's ruling of a breach of Clause 2, notwithstanding that the press release was considered to be promotional and contained language which the Appeal Board described as 'highly emotive', such as: 'reduces the risk of death by almost one third' (in the context of survival rates in childhood cancer). Accordingly, even if Genzyme's appeal on Clause 22.1 was successful, Shire reiterated that this case, Case AUTH/2528/8/12, did not warrant a ruling of a breach of Clause 2, particularly considering that the Appeal Board concluded that such a ruling was not warranted in Case AUTH/2355/9/10.

Shire cited Case AUTH/2147/7/08 as an example of where the PMCPA made rulings under Clause 7, and also considered Clause 2 (also referenced above in the context of the Clause 22.2 argument). In that case, the Panel considered that the claim for unmatched cervical cancer protection was misleading, unsubstantiated and exaggerated because there was no head-to-head data for Gardasil and Cervarix, and it was therefore not known if any of the differences between the products (based on the figures published in their respective SPCs) were clinically or statistically significant. The Panel therefore ruled breaches of Clauses 7.2, 7.4 and 7.10. The Panel also ruled breaches of Clauses 7.2, 7.4 and 7.10 in relation to other claims within the press release, and concluded that the claims disparaged Cervarix and the Department of Health's choice of Cervarix (resulting in rulings of a breach of Clauses 8.1 and 8.2). The Panel considered that the press release was non-promotional (no breach of Clause 3.2 was ruled) but agreed that it would encourage patients to seek a prescription of Gardasil (a breach of Clause 20.2, the predecessor to Clause 22.2, was ruled). Shire noted, however, that the Panel did not consider that the circumstances warranted a breach of Clause 2. Whilst Shire contested the Clause 7 rulings and distinguished the Gardasil case (Case AUTH/2147/7/08) in this regard, the cases were comparable in so far as the following features were common to both:

- The Panel ruled breaches of Clause 7 on the basis that, in its view, the press releases respectively made comparative claims of clinical and statistical significance which were not warranted in light of the absence of head-to-head data;

- The Panel considered that the material was non-promotional in nature;
- The Panel ruled that the respective press releases would encourage patients to seek a prescription for a particular prescription only medicine; and
- The respective press releases were sent to a patient organisation (in so far as could be understood from the Gardasil case report) (Case AUTH/2147/7/08).

However, Shire submitted that notwithstanding these similarities, the Panel did not rule a breach of Clause 2 in the Gardasil case (Case AUTH/2147/7/08), but ruled a breach of Clause 2 in the present case (Case AUTH/2528/8/12). If anything, even if all the rulings were accepted in the present case, the Gardasil case represented a much more flagrant set of breaches (there were many more rulings under Clause 7 as compared with the present case and – in contrast to the present case - the Panel also held the material to be disparaging).

Accordingly, Shire submitted that an analysis of previous rulings showed that the Panel had acted inconsistently with previous rulings and had therefore violated the principle of equality. Even if the Clause 7 breaches were upheld it would be inequitable for the breach of Clause 2 to be upheld given the previous rulings by the Panel.

Shire submitted that in addition to the lack of consistency with the Panel's previous rulings, Shire also refuted the breach of Clause 2 ruling because of the special circumstances at stake, namely the uncertainty regarding what was permissible in communications to patient organisations. Patient organisations had a hybrid status: as well as being advocates for, and representing the interests of patients, they also had an integral role in the scientific community in certain disease areas (including Gaucher disease). Shire was concerned that, as far as it transpired from the ruling, the Panel had taken no account of the very special role played by patient organisations in this rare disease area. Rather, the Panel appeared to assume that a patient organisation would be particularly naive and susceptible to being misled, whereas in fact the Gauchers Association was represented by highly sophisticated individuals whose unique role in this orphan disease area was set out on their website, as was noted in the Shire response to the complaint. This audience would clearly understand that confirmatory conclusions might not be drawn from exploratory findings. The Gauchers Association's introduction to the press release when reproduced on its website indicated its evaluation of the data. Even if the Panel's rulings of breaches of Clauses 7.2, 7.3, 22.2, 14.1 and 14.5 were not overturned, Shire submitted that it should nevertheless recognise that the issues at stake in this case were very much open to interpretation, such that a Clause 2 ruling – reserved for flagrant breaches of the Code – was unwarranted. In ruling a breach of Clause 2, the Panel had effectively stated that this was one of the worst possible breaches of the Code, which Shire respectfully submitted was not so. Such a ruling would be inconsistent with past practice and therefore devalue the currency of Clause 2.

**RESPONSE FROM GENZYME**

Genzyme noted that Shire raised a number of arguments to support its view that the Panel's ruling that the press release constituted a breach of Clause 2 was incorrect. The first argument was that the press release did not breach Clauses 7.2 and 7.3 of the Code. This argument was contradicted by the Panel's ruling and Genzyme's comments outlined above.

Genzyme noted that Shire also claimed that the press release did not fall within the list of examples of breaches of Clause 2 provided in the supplementary information to the clause. Although Shire acknowledged that the list of examples of breaches in Clause 2 was not exhaustive, the company claimed that a ruling of a breach of Clause 2 outside the non-exhaustive list of examples constituted an infringement of the principle of legal certainty. Genzyme disputed this argument. Clause 2 clearly identified the list of examples that it provided as not exhaustive. In such circumstances it could not be argued that a ruling of a breach of Clause 2 which fell outside the scope of these examples, violated the principle of legal certainty.

Shire's Appeal also discussed previous Panel's rulings in relation to Clause 2 of the Code. Shire argued that the rulings of a breach of Clause 2 in Cases AUTH/2404/5/11 and AUTH/2402/4/11 were not relevant for the current case. This was because these cases related to promotional materials. As highlighted a number of times, Genzyme alleged that Shire's press release was promotional. The rulings of a breach of Clause 2 in Cases AUTH/2404/5/11 and AUTH/2402/4/11 were, therefore, relevant for this specific case.

Genzyme continued to allege that the press release was promotional, and even if it was ruled not to be would not prohibit a finding that, given the misleading nature of the comparative claims that it contained, the press release constituted a breach of Clause 2. In Case AUTH/2257/8/09, for example, the Panel ruled that the distribution of non-promotional materials to a patient organisation could constitute a breach of Clause 2 if the information provided in relation to a prescription only medicine was unbalanced, misleading, had not been certified as required by Clause 14.3 of the Code and encouraged members of the public to ask their health professional to prescribe a specific prescription only medicine product. In common with the situation in Case AUTH/2257/8/09, Shire's press release was misleading, unbalanced and encouraged patients to ask their health professional to prescribe VPRIV. The Panel also ruled that the press release was not certified as required by Clause 14.3 of the Code.

Genzyme noted that Shire had provided examples of cases in which the Panel had ruled that a breach of Clause 2 of the Code had not occurred in similar situations the present case. Rulings of a breach or no breach of Clause 2 were specific to the facts of each case. Cases AUTH/2355/9/10 and AUTH/2147/7/08 cited by Shire were not fully relevant for the present case. Unlike these two cases, in

which no breach of Clause 2 of the Code was ruled, Shire's press release relied on unsound statistics to create a contrary and misleading impression that was proactively distributed by Shire to patient organisations. These cases were, therefore, irrelevant.

Genzyme disagreed with Shire's claim that the Panel's ruling of a breach of Clause 2 created uncertainty regarding what was permissible in communications with patient organisations. The Panel's ruling was specific to a particular set of facts and a particular press release, which it had concluded included misleading, unbalanced and unfair comparative and superiority claims. Such a ruling did no damage to the important underlying principle of legitimate scientific exchange. The Panel and Appeal Board simply could not permit companies to hide behind the principle of scientific exchange to circumvent the provisions of the Code prohibiting misleading communication and promotion of prescription only medicines to the public.

**APPEAL BOARD RULING**

The Appeal Board considered that Shire should have taken much greater care to ensure that the press release accurately reflected the study and its results. There had not been a new medicine in this disease area for a number of years and understandably there would be much interest from patients and their families. To present exploratory endpoints in such a way as to imply statistical and clinical significance was unacceptable. The Appeal Board noted its rulings of breaches of the Code at Points 1-7. The Appeal Board considered the content of the press release and its subsequent proactive provision to a patient organisation was wholly unacceptable and brought discredit upon, and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

**9 Compliance with all applicable codes, laws and regulations**

**COMPLAINT**

Genzyme noted Shire's assertion that it was had complied with all applicable provisions of the Code.

Genzyme stated that its complaint set forth eight concerns with the press release, all of which individually and collectively breached the Code. These included, but were not limited to:

- Distribution of promotional material within the UK without the proper certification required by Clause 14;
- Failure for the UK prescribing information to accompany the press release, in breach of Clause 4;
- Bringing discredit to, and reduction of confidence in, the Industry, in breach of Clause 2;
- Presenting information, claims and comparisons that were not balanced, fair, or based on an up-to-date evaluation of all the evidence, in breach of Clause 7.2;
- Failure to ensure that the information, claims and comparisons were based on sound statistics, in breach of supplementary information to Clause 7.2 of the Code;
- Presenting misleading comparisons, in breach of Clause 7.3 of the Code; Distributing promotion about a prescription medicine to the public, in breach of Clause 22.1 of the Code;
- Distributing publicly available information intended to encourage the public to ask their health professional to prescribe a specific prescription only medicine, in breach of Clause 22.2; and
- Failure to present information about prescription only medicines to the public in a balanced way, in breach of Clause 22.2.

Genzyme stated that this complaint was not based on a minor technical breach of the requirements of the Code, but on a systematic and comprehensive breach of at least six separate clauses of the Code. Therefore, it considered that Shire had wilfully breached Clause 1.8. Genzyme incorporated by reference all of its arguments contained above. It was important to note that it listed as the first breach the failure to comply with the requirement for certification of the press release provided for in Clause 14. Had this fundamental requirement of the Code been complied with, the press release with its clear comparative/superiority claims and misleading science would never have been issued. Flowing from this fundamental breach, the press release breached the Code in at least nine other ways. Although proper non-promotional discussion of scientific data presented in a non-misleading way remained permissible, the press release failed to meet these standards in the fundamental ways described above.

**RESPONSE**

Shire submitted that, as explained above, the content review and distribution of the press release had complied with the Code. Genzyme's allegation of a 'wilful breach' of Clause 1.8 was a very serious allegation, of potential damage to Shire's reputation, and entirely without foundation. As a responsible pharmaceutical company, Shire would never wilfully breach the Code, or any other applicable law or regulation.

In conclusion, Shire submitted that Genzyme's allegations were entirely without foundation and rejected Genzyme's allegations in full.

The press release was a non-promotional communication aimed at the investor community (potential and current), as well as relevant scientific and medical media. The presentation of the data in the press release would not encourage health professionals to prescribe VPRIV, nor was it made for the purpose of encouraging members of the public to ask their doctor to prescribe the product. As such, the press release did not require certification under the Code, nor was there any requirement to include

the prescribing information (Shire referred further to it responses to the allegations in Points 6 and 7).

Further, consistent with the poster, the press release did not draw comparisons between VPRIV and Cerezyme, nor did it make statements of clinical superiority (Shire referred further to its responses to the allegations in Points 1, 2, 3 and 5). This was neither the effect nor the intention of the press release. This was clear from the express terms of the press release and would have been understood by its readers.

**PANEL RULING**

The Panel noted Shire's submission that the press release was a global one, had appeared on its global website and had been sent to, *inter alia*, a UK patient organisation. Clause 1.8 required that pharmaceutical companies must ensure that they complied with all applicable codes, laws and regulations to which they were subject. The supplementary information to that Clause noted, *inter alia*, that activities carried out and materials used in a European country by a pharmaceutical company located in a country other than a European country must comply with the EFPIA Code as well as the national code of the country in which the activities are carried out and materials are used.

The Panel noted its rulings of breaches of the Code above and considered that by failing to comply with the UK Code, Shire had failed to meet the requirements of Clause 1.8. A breach of that clause was ruled. This ruling was appealed by Shire.

**APPEAL BY SHIRE**

Shire referred to its general comments made in its appeal at Point 1 above.

For the reasons explained in its appeals above, Shire refuted each of the Panel's rulings of breaches of the Code. As a consequence, Shire submitted that the ruling of breach of Clause 1.8, namely that it had not complied with the Code, must automatically fall away.

However, as a general comment, Shire questioned the purpose of a ruling of breach of Clause 1.8. On the basis of the Panel's ruling, it appeared that whenever a company was found in breach of any clause of the Code, it must *de facto* be in breach of Clause 1.8. A ruling of a breach of Clause 1.8 would therefore apply in all circumstances, and did not add anything of substance to a ruling. Indeed, in so far as Clause 1.8 extended beyond compliance with the Code (it required that pharmaceutical companies must ensure that they had complied with all applicable codes, laws and regulations to which they were subject), the PMCPA would not always have jurisdiction to rule a breach of Clause 1.8 (for example, it could not assess whether a company had complied with national law). Surely, therefore, like Clause 22.5 (for example), Clause 1.8 should be treated as a statement of principle in relation to a company's responsibilities, rather than a clause which could be breached.

**RESPONSE FROM GENZYME**

Genzyme referred to its general comments made in its response to Shire's appeal at Point 1 above.

Genzyme noted that Shire had argued that Clause 1.8 of the Code should be treated as a statement of principle rather than a clause which could be breached. This position was not supported by the wording of Clause 1.8. This clause contained a positive obligation to comply with the EFPIA Codes the ABPI code and all national laws and regulations. By breaching a number of clauses of the Code, Shire also breached Clause 1.8. This was because the press release was promotional and was distributed to the public in the EU.

In conclusion, Genzyme stated that it appeared that the Panel carefully considered the press release, complaint and Shire's response. With regard to the Panel's rulings which Shire had appealed, Genzyme stated that they should be upheld.

**APPEAL BOARD RULING**

The Appeal Board noted its rulings of breaches of the Code in the above; consequently it upheld the Panel's ruling of a breach of Clause 1.8. The appeal on this point was unsuccessful.

**Complaint received** **21 August 2012**

**Case completed** **15 March 2013**

# PATIENT v PFIZER

## Information about Champix

**A member of the public alleged that Pfizer had failed to warn of serious side effects of Champix (varenicline). Champix was indicated for smoking cessation.**

**The complainant stated that Champix came onto the UK market in 2006. The patient leaflet made no mention of convulsions. When the complainant took the medicine in January 2008 there was also no mention of convulsions on the leaflet. The complainant submitted that she stopped smoking within a week of starting Champix. Although the complainant was supposed to take a 12 week course, at week 10 she started to feel depressed and thought of killing herself; this was out of character. The complainant's doctor told her to stop taking Champix, and within 24 days of the last dose she had a grand-mal convulsion in her sleep and then a second less than two weeks later. She had never previously had convulsions and was subsequently diagnosed with epilepsy.**

**The complainant submitted that in 2010 following a friend's experience with Champix she asked her doctor if her convulsions were connected to the Champix; her doctor thought that they could be and told the complainant to report her epilepsy as a possible withdrawal effect of Champix.**

**The complainant provided a patient leaflet prepared by Pfizer Australia in February 2007 that stated, *inter alia*, that before taking Champix a patient should tell his/her doctor if he/she suffered from repeated fits or convulsions. The complainant stated that leaflets in Canada also mentioned seizures but there was still no mention of this in UK leaflets. The complainant stated that on 22 May 2008 the Food and Drug Administration (FDA) asked Pfizer about the link between varenicline and seizures. The prescription leaflet noted that pilots, controllers and truckers should not take varenicline from 2008 due to the risk of seizures. The complainant stated that the FDA then issued a further warning to include seizures in 2009.**

**The complainant alleged that Pfizer had failed to properly warn consumers and was primarily concerned with protecting profits, even at the expense of patients' health. The complainant stated that anti-smoking medicines might adversely affect certain individuals more than others and alleged that the scientific literature, the very place doctors looked for a warning, contained barely a hint of problems in the UK, about withdrawal symptoms seen with varenicline.**

**The complainant included a detailed discussion on the link between nicotine receptors and various central nervous system disorders. The complainant submitted that genetic mutations in these receptors might make some patients particularly susceptible to developing epilepsy.**

**The complainant stated that post-marketing clinical trials mentioned grand-mal and peti-mal seizures happening within 30 days of the last dose of varenicline. It also mentioned deaths, but as it was after last dose, Pfizer did not put these forward. This was the only information after 2 years that said anything about last dose of varenicline. Everywhere seemed to state that there were no side effects from Champix after the last dose.**

**The complainant stated that Pfizer had told her on several occasions that no seizures were seen in any clinical trial involving the correct dose. When the complainant asked her first neurologist, in 2010 if she thought that Champix could have triggered epilepsy, her exact words were 'I am not prepared to put my job on the line by answering that question'. The complainant was very angry by this answer and found that Pfizer funded projects for the local NHS, so was it a case of don't bite the hand that feeds you. The complainant noted other possible conflicts of interest between Pfizer and other organizations.**

**The complainant alleged that she and others had, and still were, suffering the effects of Champix. They were given no warning of these side effects of this medicine, had reported it through the correct channels, and still nothing had been done. In the US a class action had been brought against Pfizer for $150 million for no warning of side effects. The complainant would like help to prove that Pfizer had breached the Code and that by giving no warning, it had put the public at risk.**

**The detailed response from Pfizer is given below.**

**The Panel noted that the complainant had provided much material and comment. Patient safety was extremely important. The Panel's role was to consider the allegations in relation to the requirements of the Code. In this regard, the Panel considered that the key issue raised by the complainant was that patient leaflets for Champix produced by Pfizer were misleading in relation to the risk or otherwise of convulsions associated with the use and/or discontinuation of the medicine.**

**The Panel noted that the complainant referred to 'leaflets' for Champix but it was unclear whether she had seen the summary of product characteristics (SPC), the leaflet that accompanied the medicine (PIL) or some other patient leaflet produced by Pfizer. No examples of UK materials were provided by the complainant. The Panel further noted that the PIL and SPC were regulatory documents, the content**

**of which was governed by the relevant EU or UK regulatory authority. The Code was clear that neither SPCs nor the leaflet that accompanied a medicine (PIL) were included in the definition of promotion. The contents of such documents were covered by regulations. However, Pfizer had submitted that it had also produced further leaflets, for both patients and health professionals, based on the PIL and SPC for Champix. The Panel considered that the content of these was within the scope of the Code and had to comply with it. Such material had to accurately reflect the SPC.**

**The Panel noted the complainant stated that she started a 12 week course of Champix in January 2008 which was discontinued after 10 weeks. The SPC submitted by Pfizer as current at that time (which was approved in April 2007) did not refer to fits or seizures in Section 4.8, Undesirable effects. Section 4.4, Special warnings and precautions for use, stated that there was no clinical experience with Champix in patients with epilepsy.**

**Pfizer submitted an additional patient leaflet for Champix that was available when the complainant took the medicine (prepared November 2007). One section, entitled 'What side effects might I experience?', referred to side effects associated with giving up smoking, including mood changes, sleeplessness, difficulty concentrating, decreased heart rate and increased appetite or weight gain. Common side effects for Champix were also stated, including nausea, headache, difficulty sleeping and abnormal dreams. Reference was also made to dizziness and sleepiness. Similarly to the SPC, there was no mention of fits or seizures.**

**The Panel noted that the current Champix SPC (13 April 2012) again referred in Section 4.4, Special warnings and precautions for use, to lack of clinical experience with Champix in patients with epilepsy. There was no reference to seizures or fits in Section 4.8, Undesirable effects. A current patient leaflet produced by Pfizer (prepared October 2012) referred to similar side effects as the previous patient leaflet and, in addition, to changes in behaviour and thinking, depression and anxiety, worsening of psychiatric illness and suicidal thoughts and attempts. Again there was no reference to seizure or fits.**

**The Panel noted that the complainant had submitted a patient leaflet from Australia dated February 2007 which referred to seizures and fits and advised the patient to seek immediate medical help if these were experienced. The Panel further noted Pfizer's submission that this leaflet was common to Australia and New Zealand and that the New Zealand datasheet did not refer to seizures or fits.**

**The Panel noted that the reference to seizures and fits in the Australian/New Zealand document dated February 2007 had, according to Pfizer, been made in error and had been removed in September 2007. The complainant had stated that her treatment course began in January 2008. The Panel noted that there was no reference in UK regulatory documents (SPC and PIL), either currently or when the complainant took Champix, that Champix treatment, or discontinuation of treatment, was associated with seizures or fits. The Panel further noted Pfizer's submission that there was currently no evidence of a causal relationship between varenicline and seizure. The Panel thus considered that failure to refer to seizures or fits in any Pfizer-produced patient leaflets for the UK was not a failure to reflect the available evidence about these side effects. No breach of the Code was ruled. Not referring to fits and seizures in Champix patient material did not render that material incorrect or unbalanced and no breach of the Code was ruled. The Panel noted its rulings above and subsequently ruled no breach of the Code including Clause 2. The complainant appealed all the Panel's rulings.**

**The Appeal Board considered that patient safety was extremely important. The Appeal Board noted that this was a highly personal and important issue for the complainant and it did not doubt her sincerity on the matter. The complainant had submitted a large volume of information and had referred to the conduct of other organisations. The Appeal Board noted that the complainant stated in response to a question at the appeal that she had sent all of her documents in this case to the MHRA. The Appeal Board noted that its only role was to consider matters in relation to the requirements of the Code and specifically the Panel's rulings of no breach of the Code. As stated in the introduction to the PMCPA Constitution and Procedure, the complainant had the burden of proving their complaint on the balance of probabilities.**

**The Appeal Board examined two documents which were current when the complainant was prescribed Champix. The Champix SPC (reviewed 26 April 2007) stated in Section 4.4, Special warnings and precautions for use, that there was no clinical experience with Champix in patients with epilepsy. Section 4.8 of the same SPC, Undesirable effects, did not refer to seizures, epilepsy or fits. The Appeal Board noted that the SPC and the PIL were regulatory documents and their contents were agreed with the regulators, the MHRA and the EMA. The PIL was based on the agreed SPC. The Pfizer leaflet entitled 'Information for patients who have been prescribed Champix (varenicline tartrate)' (prepared in November 2007) had to reflect the SPC and PIL and not be inconsistent with those regulatory documents. The Appeal Board noted that the Pfizer leaflet similarly did not refer to seizures, epilepsy or fits in the section headed 'What side effects might I experience'. The Pfizer leaflet did not state that there was no clinical experience with Champix in patients with epilepsy; the Appeal Board, however, did not consider that the Pfizer leaflet was inconsistent with the SPC in that regard.**

**The Appeal Board noted that the current Champix SPC did not refer to seizures, epilepsy or fits as possible adverse effects and so similarly neither did the current PIL.**

**The Appeal Board noted that the complainant had provided the Drug Analysis Print (DAP) for Champix which listed spontaneously reported adverse events**

**reported in the UK from 1 July 1963 to 18 December 2012. The report run date was 19 December 2012. The earliest reaction date was 26 December 2006. The document provided by the complainant stated that the report recorded where at least one suspected adverse drug reaction (ADR) report had been received that specified the product as a 'suspected drug' (ie suspected causal association with the reaction). It further stated that suspected ADR reports sent to the Yellow Card scheme were called spontaneous reports.**

**In this regard the Appeal Board noted the section 'seizures and seizure disorders NEC [not elsewhere classified]' gave a combined total of 74 for convulsions, epilepsy, partial seizures and status epilepticus. Other sections of the DAP recorded 3 reports of petit mal epilepsy and 15 of grand mal convulsions. The Appeal Board noted that no evidence had been provided to show that this was more than might normally have occurred in the general population who had not taken Champix. The Appeal Board noted that the DAP did not break down the data and there was no record of the situation in January 2008 when the complainant took Champix. The Appeal Board noted that the listing of an adverse event in the DAP did not prove that it had been caused by Champix. It was a record that the adverse event had happened in a patient who at the same time was taking Champix and that it *might* be causally related.**

**The Appeal Board noted that it was the role of the relevant EU or UK regulatory authority to decide the wording of SPCs and PILs. The wording of an SPC was likely to change over time as experience with a medicine grew. In that regard the Appeal Board noted correspondence between the complainant and the MHRA and in particular an email from the MHRA dated 1 October 2012 which stated that cases of seizures and epilepsy reported for varenicline (Champix) would be reviewed within the European regulatory framework in the next couple of months. It was important that the MHRA was provided with all relevant information and the complainant stated to the Appeal Board that she had provided all of her documents to the MHRA. At the appeal hearing the Appeal Board queried the accuracy of some aspects of the material submitted by the complainant and the conclusions drawn.**

**The Appeal Board noted that the complainant had provided a copy of a leaflet prepared by Pfizer Canada Inc (last revised 14 December 2011). Under a heading 'Warnings and precautions' patients were advised not to engage in potentially hazardous tasks such as driving or operating machinery as some people had reported, among other things, blackouts and seizures. Such events, however, were not included in the section of the leaflet headed 'Side effects and what to do about them'. The US full prescribing information (revised December 2012) listed convulsion as a rare side effect. Neither the Canadian nor the US document specifically included the word 'epilepsy'. The Appeal Board also noted that the patient leaflet from Australia (dated February 2007) referred to seizures and fits. Pfizer had submitted that this leaflet was used in both Australia and New Zealand and that the New Zealand data sheet did not refer to seizures or fits. Pfizer had submitted that the reference to seizures and fits in the Australian/New Zealand document had been an error and had been removed in September 2007.**

**The Appeal Board noted that the information provided by Pfizer in the UK reflected the information in the SPC and PIL which had been agreed with the UK regulatory authorities. The Appeal Board considered that it had not been provided with any evidence to show that the information Pfizer had provided to patients taking Champix in January 2008 when the complainant took Champix, was inconsistent with the evidence available at that time with regard to the possibility of developing epilepsy as a consequence of taking or stopping treatment with Champix. Therefore the failure to refer to seizures or fits in Pfizer produced patient leaflets for the UK available in January 2008 was not a failure to reflect the available evidence. Thus the Appeal Board upheld the Panel's ruling of no breach of the Code. The appeal on this point was unsuccessful.**

**Similarly the Appeal Board considered that it had not been provided with any evidence to show that information provided to the public by Pfizer in January 2008 was not factual or balanced with regard to the side-effect profile of Champix. Not referring to fits and seizures in Pfizer produced patient leaflets did not mean that this material was incorrect or unbalanced. Thus the Appeal Board upheld the Panel's ruling of no breach of the Code. The appeal on this point was unsuccessful.**

**The Appeal Board noted its rulings above and consequently upheld the Panel's ruling of no breach of the Code was ruled including Clause 2. The appeal on this point was unsuccessful.**

A member of the public alleged that Pfizer had failed to warn of serious side effects of Champix (varenicline). Champix was indicated for smoking cessation.

**COMPLAINT**

The complainant stated that Champix came onto the UK market in 2006. The patient leaflet made no mention of convulsions. The complainant took the medicine in January 2008, at which time there was also no mention of convulsions on the leaflet. The complainant submitted that she stopped smoking within a week of starting Champix. The complainant stated that she was supposed to take a 12 week course but at week 10 she started to feel depressed and thought of killing herself; this was out of character. The complainant was told by her doctor to stop taking Champix, and within 24 days of the last dose she had a grand-mal convulsion in her sleep. She had never had a convulsion. The complainant stated that she then had a second one in her sleep within two weeks of the first one and was subsequently diagnosed with epilepsy.

The complainant submitted that in 2010 a friend was told that he was not suitable for Champix as he had a history of head injury and that it might cause a seizure. The complainant then contacted her doctor to see if her convulsions were connected to the Champix, her doctor thought that they could be and told the complainant to report her epilepsy as a possible withdrawal effect of Champix.

The complainant stated that this was when she started her research and submitted a patient leaflet that was prepared by Pfizer Australia in February 2007. This leaflet stated, *inter alia*, that before taking Champix a patient should tell his/her doctor if he/she suffered from repeated fits or convulsions. The complainant stated that leaflets in Canada also mentioned seizures but there was still no mention of this in UK leaflets. The complainant stated that on 22 May 2008 the Food and Drug Administration (FDA) asked Pfizer about the link between varenicline and seizures. The prescription leaflet noted that pilots, controllers and truckers should not take varenicline from 2008 due to the risk of seizures. The complainant stated that the FDA then issued a further warning to include seizures in 2009.

The complainant alleged that Pfizer had failed to properly warn consumers and was primarily concerned with protecting profits, even at the expense of the health of those trying to quit smoking to prolong their lives. The complainant submitted that genetic engineering altered DNA in ways which would never occur in nature. These mutations could easily cause unforeseen complications, such as formation of toxins or allergens. The effects of these problems might not be easy to detect. The complainant stated that medicines of this nature might adversely affect certain individuals more than others and alleged that the scientific literature, the very place doctors looked for a warning, contained barely a hint of problems in the UK and almost stated that no withdrawal symptoms were seen with varenicline.

The complainant stated that varenicline was developed by Pfizer Inc in 1997; it was based on the naturally-occurring alkaloid cytisine which was extracted from the seeds of the Laburnum, (Golden Rain), a shrub or small tree. It was one of the Laburnum anagyroides, or Latin name *Leguminosae/Fabaceae*. The seeds also contained proteins, tannins, glycosides and choline. Cytisine was isolated and used in pharmaceutical preparations to treat, for example, hypotension. The complainant stated that in homeopathy a tincture prepared from the fresh leaves and flowers was sometimes used to treat various neurological and digestive disorders. Laburnum was classed as a dangerous plant; it should never be collected and used for self-medication as the seeds were highly toxic due to cytisine content. Symptoms of cytisine poisoning included dilation of the pupils, stomach cramps, vomiting, giddiness, muscular weakness, convulsions, respiratory failure and death. These were all signs of a neurotoxin, most being the reactions one would have to snake venom.

The complainant stated that a clinical trial, Bonn *et al*, sponsored by Pfizer and GlaxoSmith [sic] resulted in the creation of cytisine 27, generic name for Tabex, (which was patented and marketed and produced by GlaxoSmith [sic]) and the creation of the cytisine analogue varenicline, a DNA copy of cytisine (this was not a naturally occurring alkaloid). This was then patented by Pfizer and marketed and produced as Chantix in Canada and the US and as Champix in the UK.

The complainant alleged that nicotinic acetylcholine receptors (nAChRs) had been implicated in a number of disorders affecting the nervous system (eg Tourette's syndrome, schizophrenia, epilepsy, depression, anxiety) as well as pathologies in non-neuronal tissues and cells (eg small-cell lung carcinoma or inflammatory bowel disease). However, the main focus in the field of these ligand-gated ion channels was on their involvement in neurodegenerative diseases such as Alzheimer's or Parkinson's and in antinociception. The complainant stated that the etiology of this neuropsychiatric disorder and the mechanism of the beneficial effect of nicotine remained unclear. It was observed that the density of alpha-7 receptors had been reduced in the CA3 region of hippocampus in the brain of schizophrenics.

All this information was from a paper published by the Pfizer group in 2000. There was knowledge of a link. Dinucleotide polymorphism at chromosome 15q13-14, a site of the alpha-7 subunit gene CHRNA7, had been found. Epilepsy, in particular, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), epileptic seizures occurring mainly during the sleep, was associated with mutation in the gene coding for either the alpha-4 or beta-2 nAChR subunit. These mutations had been reported to be responsible only for some factors leading to the clinical manifestation of the disease, however, not for all the symptoms of ADNFLE. There were experimental indications that also alpha-7 subunits were involved in seizure control.

The complainant stated that depression/anxiety were also believed to be related to nAChR dysfunction. Direct evidence of altered nAChR function in individuals suffering from these disorders was missing, but genetic studies showed a positive correlation between tobacco dependence and major depression. In addition, smoking was more prevalent in patients suffering from depression than in the general population.

Alzheimer's disease was a neurodegenerative disease characterised by a progressive loss of short-term memory and higher cognitive functions. The most marked changes in the neurotransmitter system of patients were the degeneration of the cholinergic innervation and the reduction of the choline acetyl transferase activity in the hippocampus and cerebral cortex. There was accumulating evidence that the function and density of neuronal nAChRs (especially alpha-4-beta-2 subtype) was reduced in the brains of Alzheimer's patients. In addition beta-amyloid peptides, which were part of the neuritic plaques found in the brains of Alzheimer's patients, had been shown to bind to alpha-7 nAChRs and were neurotoxic. Thus, medicines targeted for treatment of Alzheimer's

disease, through modulation of nAChRs, should either targ*et al*pha-4-beta-2 subtype and cause receptor activation or activate alpha-7 and improve cell survival.

The complainant noted that patients with Parkinson's disease suffered from motor dysfunction which resulted in muscular rigidity, tremor and uncoordinated movement. Parkinson's disease was a neurodegenerative disease manifested by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta accompanied by parallel loss of high affinity nicotine binding in these regions. Nicotine improved the symptoms of Parkinson's disease and the beneficial effects of the tobacco alkaloid were consequences of increased dopamine levels in the substantia nigra and mesolimbic system, as well as of possible inhibition of monoamine oxidase B. The complainant stated that the risk of developing Parkinson's disease was inversely correlated with the number of cigarettes smoked.

The complainant submitted that pain and nAChRs were linked since the discovery of antinociceptive properties of the nicotine agonist epibatidine, which possessed a 200-fold higher analgesic effect than morphine in the hot-plate test. The complainant stated that the initial euphoria of this discovery disappeared because of the highly toxic effects of epibatidine mediated by peripheral nAChRs. Conversely, ABT-594, a selective nicotinic agonist for neuronal subtypes had been reported to be in clinical trials for the treatment of neuropathic pain, even if the side effect profile of this compound was not improved compared with epibatidine. The complainant stated that tobacco smoking, despite its positive effect in etiology of diseases such as Alzheimer's or Parkinson's, was the leading cause of preventable death worldwide. Nicotine mediated its action through nAChRs in the central nervous system especially via dopamine release in the nucleus accumbens or prefrontal cortex. These brain regions were connected to the ventral tegmental area that was a part of the reward system in the human brain. Nicotine administration in a form of gum, transdermal patch, nasal spray and inhaler or the non-nicotine based antidepressant bupropion was used for the treatment of nicotine addiction. Administration of nicotine by any form was statistically more effective than placebo, but the long-term relapse rates were as high as 80%. Thus, improving the long-term efficacy was a key component of novel pharmacotherapies for smoking cessation.

The complainant stated that human post-marketing clinical trials mentioned grand-mal and peti-mal seizures happening within 30 days of the last dose of varenicline. It also mentioned deaths, but as it was after last dose, Pfizer did not put these forward. This was the only information after 2 years that said anything about last dose of varenicline. Everywhere seemed to state that there were no side effects from Champix after the last dose.

The complainant stated that she had contacted Pfizer UK on several occasions and the company had told her that no seizures were seen in any clinical trial involving the correct dose. The complainant then found, with help from her MP, that many members of Parliament and of the House of Lords had shares, private interests or other links with pharmaceutical companies including Pfizer. Also Pfizer sponsored a lot of projects within the NHS. When the complainant asked her first neurologist in 2010 if she thought that Champix could have triggered epilepsy, her exact words were 'I am not prepared to put my job on the line by answering that question'. The complainant was very angry by this answer and found that Pfizer funded projects in the local NHS, so was it a case of don't bite the hand that feeds you. The complainant noted other possible conflicts of interest between Pfizer and other organisations. The complainant stated that she had set up a petition on the subject of conflict of interest and needed 100,000 signatures for it to be listened to in the House of Lords.

The complainant alleged that she and others had, and still were, suffering the effects of Champix. They were given no warning of these side effects of this medicine, had reported it through the correct channels, and still nothing had been done. In the US a class action had been brought against Pfizer for $150 million for no warning of side effects. The complainant alleged that Pfizer had breached the Code and that by giving no warning, it had put the public at risk. The complainant wanted to sue and the money to be put back into the NHS.

When writing to Pfizer the Authority asked it to respond in relation to the requirements of Clauses 2, 7.9, 9.1 and 22.2.

**RESPONSE**

In reviewing the complaint, Pfizer submitted that it was important first to separate out from its content which aspects fell within the scope of the Code. Pfizer proposed that the following information was out of scope of the Code.

Cytisine

- Information on genetic engineering and the plant *Laburnum*, the seeds of which contain cytisine; cytisine had a molecular structure similar to that of nicotine and varenicline – as the complainant has noted, the concept for varenicline in early drug discovery was based partly on cytisine.
- Details provided regarding the 'creation' of cytisine 27 (Tabex) – this medicine was not produced by Pfizer; the complainant noted that Tabex was patented, marketed and produced by GlaxoSmith [sic]. Pfizer could find no information to confirm this, desk research indicated it was produced by Sopharma AD in Bulgaria, and leading key opinion leaders had published a paper on Tabex as an aid to smoking cessation for the past 40 years, having been licensed in Eastern Europe (Zaatonski *et al* 2006). There was insufficient information on its effectiveness to warrant licensing by modern standards.

Role of nAChRs in human pathology

- The information provided was about the role of nAChRs in human pathology and the perceived link with varenicline. No causal link had been

established to demonstrate that varenicline caused schizophrenia, Tourette's syndrome, epilepsy, depression and anxiety, or the neurodegenerative Alzheimer's and Parkinson's diseases. It was unclear as to which paper the complainant had referred in the statement 'This information was from a paper published by the Pfizer group in 2000. There was knowledge of link'. Pfizer took the safety of all its medicines seriously and conducted ongoing programmes of clinical research and global surveillance of spontaneous reports to monitor and assess the safety of its medicines. All of this information was shared with worldwide medicine regulators, including the European Medicines Agency (EMA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

Patient information

- Pfizer could not comment on the individual patient's clinical history or why the complainant's friend was/was not prescribed varenicline by his doctor.

Notes and comments

- Potentially disparaging comments were indicated about the patient's neurologist and others – these were outside the scope of the Code and it would not be appropriate for Pfizer to comment, for example, on a private conversation between the complainant and her neurologist (ref: 'I am not prepared to put my job on the line by answering that question.').

**General allegations**

Pfizer submitted that the patient's general allegation was that Pfizer had failed to provide comprehensive information about the safety profile of varenicline. The main safety issue the complainant appeared to focus on was that of seizure. Pfizer worked closely with worldwide regulators to monitor and review all sources of data for varenicline, including post-marketing reports of adverse events on an ongoing basis. Currently there was no scientific evidence to demonstrate a causal relationship between varenicline and seizure.

The complainant included a leaflet from Australia that appeared to be patient information, prepared in February 2007. 'Seizures or fits' were included in the 'Side effects' section, as follows:

> 'If any of the following happen, tell your doctor immediately or go to A&E at your nearest hospital: wheezing, difficulty in breathing or shortness of breath; severe chest pain; seizures or fits; fainting; swelling of the face, lips, mouth, tongue or throat; severe sudden onset of itchy swellings on the skin; and severe skin reaction with painful red blisters with chills, fever, aching muscles and generally feeling unwell.'

The current consumer medicine information (CMI) for varenicline in Australia, updated in December 2010, did not contain the same information, and was therefore not different to the UK patient information leaflet (PIL) in that regard. It mentioned areas in which varenicline had not been studied, including repeated fits or convulsions (epilepsy), in line with that of the UK varenicline summary of product characteristics (SPC). With regard to adverse effects, there was no listing for epilepsy, convulsion or seizures. An analysis of post-marketing adverse effects reports received by the US FDA, conducted by the Institute for Safe Medication Practices (ISMP), was also included in the complainant's letter. As the authors themselves concluded, whilst reports of side effects of varenicline, including skin reactions and seizures, were received, these did not establish causality and only identified potential causes.

Pfizer stated that the basis of its response to this complaint was in relation to the safety and tolerability materials which had been developed for varenicline. These were materials that could be provided to health professionals together with information provided to smokers by their health professional in the form of a patient tear-off information sheet. In addition, the PIL provided essential information which included special warnings and precautions, side effects and dosing. This enabled smokers to use the medicine appropriately and gain the most benefit whilst maximising patient safety. Pfizer had a responsibility to ensure that in all information provided either to health professionals or patients was consistent with the SPC, was accurate, balanced, up-to-date, not misleading or exaggerated, and was capable of substantiation.

**Patient information leaflet**

Pfizer noted that as for centrally approved products, the PIL was approved by the European Medicines Agency (EMA) in line with Title V (Labelling and Package Leaflet) of the Council Directive 2001/83/EC. Pfizer submitted that the Champix PIL provided a clear overview of the medicine's safety and tolerability profile (a copy was provided). It clearly stated from the outset that the patient should read the information before starting the medicine. Additionally, it referred the patient to their health professional for any further clarification or the onset of any serious side-effects, or side effects not reported within the document.

Pfizer submitted that the PIL provided a clear overview of the indication for varenicline under the heading 'What is Champix and what is it used for'. The section entitled 'Before you take Champix' provided the patient with an overview of the contra-indications together with the special warnings and precautions for varenicline. The special warnings and precautions section provided an overview of the neuropsychiatric and cardiovascular events reported in patients taking varenicline with clear guidance to seek immediate support from their doctor in the event of any changes in symptoms. This section also made the patient aware of the potential effects of stopping smoking, discontinuing varenicline and interactions with other medicinal products. The safety profile of varenicline in pregnancy and breast feeding together with its use while driving and operating machinery were all clearly documented within the PIL. The dosage, including dose, frequency, and duration of treatment together with guidance on what action to take if the patient missed

a dose or accidentally overdosed was captured within this document.

Pfizer submitted that a detailed account of the possible side effects of varenicline including: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000) were all documented within the PIL. Importantly, this section highlighted the importance for the patient to stop treatment and contact their doctor immediately if they experienced neuropsychiatric symptoms, swelling of the face, mouth or throat or if their skin started to peel or blister. In summary, Pfizer stated that the Champix PIL provided a clear overview of the safety and tolerability profile with guidance to seek support from a doctor/pharmacist in certain circumstances. The PIL was consistent with the SPC and was legible, clear, easy to use and enabled the user to act appropriately.

**Patient tear-off information sheet**

Pfizer submitted that a patient tear-off information sheet, which health professionals could provide to patients, was also consistent with the SPC. The indication for varenicline, together with its contra-indications, were clearly stated under the heading 'Am I suitable for Champix?'. Furthermore, a section entitled 'What side effects might I experience?' provided an overview of some of the common side effects of varenicline and some of the common withdrawal symptoms associated with smoking cessation. The effects of varenicline on the ability to drive and use machinery were described. Within this section, the special warnings and precautions in relation to neuropsychiatric and cardiovascular disease were addressed. The importance of stopping medication and seeking support from a doctor should such symptoms arise was also highlighted.

Pfizer stated that in addition, patients were advised to seek their health professional's support should they be concerned about any side effects, if the side effects became serious, or if the patient noticed side effects not in the package leaflet. The list of side effects reported in the tear-off sheet was not exhaustive and there was clear guidance that the patient should refer to the PIL for other side effects that had been reported. Regarding potential interactions with other medicines, there was also a section entitled 'Can I take Champix with my other medication?'. This was consistent with the SPC for varenicline and in addition provided the patient with information regarding the effects of stopping smoking on other medicines which might require dose adjustment.

Pfizer submitted that another important area for consideration was the dosage of varenicline and this was addressed in the material providing the patient with information on the dose, frequency, duration of treatment and also guidance on what to do should the patient miss a dose. In summary, this patient information sheet provided a clear overview of the key features of the SPC to ensure that the patient was aware of the safety and tolerability profile of varenicline.

Pfizer noted that the item was a pad to be distributed to health professionals and therefore included varenicline prescribing information. The tear-off sheets were only provided to patients already prescribed varenicline, and the information sheets, once torn from the pad, did not include prescribing information.

**Safety and tolerability folder**

Pfizer stated that for further education for health professionals around the safety and tolerability of varenicline, Pfizer had also generated a specific folder to raise awareness of its safety profile (a copy was provided). Pfizer noted the use of the black triangle to denote that special reporting was required in relation to adverse reactions. The folder provided an overview of the very common side effects reported with an incidence of ≥10% for varenicline, together with the common symptoms of nicotine withdrawal. There was clear guidance for the health professionals as to the frequency of these adverse events together with the severity and discontinuation rates due to adverse events compared with placebo. Further information regarding interactions with other medicines was also documented.

Pfizer submitted that the special warnings and precautions for varenicline in relation to neuropsychiatric and cardiovascular issues and clarification for health professionals to stop treatment immediately if such symptoms arose had been effectively communicated, and was consistent with the SPC. As the folder did not cover all aspects from the SPC there was an additional clear statement referring health professionals to the SPC for further information on the safety profile of varenicline. This document was consistent with the SPC, accurate, balanced, up-to-date, not misleading or exaggerated and capable of substantiation.

Pfizer stated that the material which had been generated by Pfizer for health professionals and patients was at all times consistent with the SPC, accurate, balanced, up-to-date, not misleading or exaggerated and capable of substantiation. The material had been generated to maintain patient safety by ensuring accurate communication of the safety and tolerability profile of varenicline for health professionals and for patients. The patient-specific material provided key information as to what the patient could expect from taking varenicline. In addition, it clearly stated what action needed to be taken regarding any neuropsychiatric or cardiovascular symptoms or any side effects that were of a concern to the patient which might arise while taking the medicine.

Pfizer considered that the materials communicating the safety of varenicline both to health professionals and to patients had not brought discredit upon, or reduced confidence in, the pharmaceutical industry and therefore that Clause 2 had not been breached. Pfizer submitted that as evident from the material provided, it had at all times provided a consistent, accurate and balanced reflection of the information from the varenicline SPC regarding the safety and tolerability profile. Pfizer had never implied that

varenicline was safe and had provided a clear overview of the indication, contra-indications, special warnings and precautions in relation to neuropsychiatric and cardiovascular events, dosing regimen, potential side effects and interactions for varenicline. Pfizer denied a breach of Clause 7.9.

Pfizer considered that high standards had been maintained at all times in the generation of the material for health professionals and patients to ensure that it was consistent with the SPC in relation to the safety and tolerability profile of varenicline. Pfizer denied a breach of Clause 9.1.

Pfizer stated that the material generated about the current safety and tolerability of varenicline had always been factual and presented in a balanced way. It did not raise unfounded hopes of successful treatment and was not misleading with respect to the safety of the product. It had been generated to ensure that health professionals and patients were aware of the safety and tolerability profile of varenicline to support patient safety and appropriate prescribing. Pfizer denied a breach of Clause 22.2.

Pfizer stated that in summary, the safety and tolerability material generated for varenicline provided an overview as to what a patient could expect from taking varenicline including common adverse events, special warnings and precautions and was fully consistent with the SPC. Pfizer had always provided comprehensive information about the side effect profile of varenicline and therefore strongly denied any breach of Clauses 2, 7.9, 9.1 or 22.2.

Following a request for further information, Pfizer submitted that the previously supplied PIL was approved in April 2007. Two earlier versions of the PIL were provided. The first was approved in September 2006 and was in varenicline packs December 2006 - July 2007. The second was approved in February 2007 and was in varenicline packs July 2007 - May 2008.

Pfizer stated that varenicline received marketing authorization in the EU on 26 September 2006 via a centralised procedure. Varenicline labelling, including the SPC and package leaflet was therefore consistent across the EU.

Pfizer submitted that during 2006 and 2007 there were both type I and type II variations, as well as notifications that led to changes in the varenicline SPC and package leaflet. During 2008 there were substantive updates to the varenicline labelling, including the SPC and package leaflet. These occurred subsequent to January 2008 and related primarily to neuropsychiatric events and hypersensitivity reactions. Between 2006 and 2008 there were no changes to the UK SPC or PIL with regard to seizures or epilepsy. Throughout this time the SPC stated in Section 4.4 'There is no clinical experience with CHAMPIX in patients with epilepsy'. Seizures or fits were not listed in Section 4 'Undesirable effects' in either the UK PIL already submitted (April 2007) or in the PILs provided subsequently.

Pfizer stated that it had contacted Pfizer Australia/New Zealand about the reference to seizures on the CMI leaflet from Australia/New Zealand dated February 2007. The varenicline CMI was a common document used in both Australia and New Zealand. Varenicline was launched in New Zealand in April 2007 with the CMI dated February 2007. The CMI was revised in September 2007, in which 'seizures or fits' was deleted to ensure consistency with the data sheet in New Zealand. The data sheet was the New Zealand equivalent of the SPC, and 'seizures or fits were not listed in the SPC. Varenicline was not launched in Australia until December 2007 and used the CMI dated September 2007 (ie not the February 2007 CMI).

Following a request for further information, Pfizer submitted that, regarding product labelling in Australia and New Zealand, there were separate health authorities. In Australia it was the Therapeutic Goods Administration (TGA) and in New Zealand the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE). The core labelling documents ('PI' in Australia; 'datasheet' in New Zealand) were different for each country. The CMIs, however, were common to both countries, hence the joint Australia/New Zealand addresses on the documents. CMIs were released through an organisation called Heathlinks in Australia. In New Zealand CMIs were made available through MEDSAFE.

Varenicline was launched in Australia in December 2007, with the September 2007 CMI. The February 2007 CMI was never released via Healthlinks in Australia, but might have been provided to those who participated in an Australian patient familiarisation program which ran in the second half of 2007. Varenicline was launched in New Zealand in April 2007, with the February 2007 CMI (made available on the MEDSAFE website). The CMIs did not go into packs in Australia or New Zealand but would have been available electronically in New Zealand at launch. It was therefore possible that the complainant obtained the CMI electronically when it was live in New Zealand but not issued in Australia.

The New Zealand datasheet did not refer to seizures or fits. Pfizer submitted that unfortunately its records did not show why these terms were included in the CMI, but the most likely explanation was that this was an oversight. This was rectified as soon as the discrepancy between the CMI and the datasheet was discovered. The CMI must reflect what was in the product datasheet so reference to 'seizures and fits' in the CMI was removed when the discrepancy between the CMI and product datasheet was noted.

**PANEL RULING**

The Panel noted that the complainant had provided much material and comment. Patient safety was extremely important. The Panel noted that the complainant stated that she had provided information to her doctor who advised her to report her epilepsy as a possible withdrawal effect of Champix. It was not clear whether the complainant had done so although she had contacted Pfizer about the matter. The pharmacovigilance procedures at

Pfizer should have ensured that the relevant data was added to its possible adverse event database. Pfizer had not stated whether this was so but in that regard the Panel noted that the company did not know the complainant's identity. The complainant's doctor also had a role in reporting the matter following any discussion with the complainant about the possibility of the complainant's seizures being linked to Champix. The Panel's role was to consider the allegations in relation to the requirements of the Code. In this regard, the Panel considered that the key issue raised by the complainant was that patient leaflets for Champix produced by Pfizer were misleading in relation to the risk or otherwise of convulsions associated with the use and/or discontinuation of the medicine.

The Panel noted that the complainant referred to 'leaflets' for Champix but it was unclear whether she had seen the PIL or SPC, or some other patient leaflet produced by Pfizer. No examples of UK materials were provided by the complainant. The Panel further noted that the PIL and SPC were regulatory documents, the content of which was governed by the relevant EU or UK regulatory authority. Clause 1.2 of the Code was clear that neither SPCs nor the leaflet that accompanied a medicine (PIL) were included in the definition of promotion. The contents of such documents were covered by regulations. However, Pfizer had submitted that it had also produced further leaflets, for both patients and health professionals, based on the PIL and SPC for Champix. The Panel considered that the content of these was within the scope of the Code and had to comply with it including, in particular, Clauses 7 and 22. Such material had to accurately reflect the SPC.

The Panel noted the complainant stated that she started a 12 week course of Champix in January 2008 which was discontinued after 10 weeks. The SPC submitted by Pfizer as current at that time (which was approved in April 2007) did not refer to fits or seizures in Section 4.8, Undesirable effects. Section 4.4, Special warnings and precautions for use, stated that there was no clinical experience with Champix in patients with epilepsy.

Pfizer submitted an additional patient leaflet for Champix that was available when the complainant took the medicine (ref SCE055, prepared November 2007). One section, entitled 'What side effects might I experience?', referred to side effects associated with giving up smoking, including mood changes, sleeplessness, difficulty concentrating, decreased heart rate and increased appetite or weight gain. Common side effects for Champix were also stated, including nausea, headache, difficulty sleeping and abnormal dreams. Reference was also made to dizziness and sleepiness. Similarly to the SPC, there was no mention of fits or seizures.

The Panel noted that the SPC submitted by Pfizer as the current Champix SPC (13 April 2012) again referred in Section 4.4, Special warnings and precautions for use, to lack of clinical experience with Champix in patients with epilepsy. There was no reference to seizures or fits in Section 4.8, Undesirable effects. A current patient leaflet produced by Pfizer (ref CHA1413, prepared October 2012) referred to similar side effects as the previous patient leaflet and, in addition, to changes in behaviour and thinking, depression and anxiety, worsening of psychiatric illness and suicidal thoughts and attempts. Again there was no reference to seizure or fits.

The Panel noted that the complainant had submitted a patient leaflet from Australia dated February 2007 which referred to seizures and fits and advised the patient to seek immediate medical help if these were experienced. The Panel further noted Pfizer's submission that this leaflet was common to Australia and New Zealand and that the New Zealand datasheet did not refer to seizures or fits.

The Panel noted that the reference to seizures and fits in the Australian/New Zealand document dated February 2007 had, according to Pfizer, been made in error and had been removed in September 2007. The complainant had stated that her treatment course began in January 2008. The Panel noted that there was no reference in UK regulatory documents (SPC and PIL), either currently or when the complainant took Champix, that Champix treatment, or discontinuation of treatment, was associated with seizures or fits. The Panel further noted Pfizer's submission that there was currently no evidence of a causal relationship between varenicline and seizure. The Panel thus considered that failure to refer to seizures or fits in any Pfizer-produced patient leaflets for the UK was not a failure to reflect the available evidence about these side effects. No breach of Clause 7.9 was ruled. Not referring to fits and seizures in Champix patient material did not render that material incorrect or unbalanced and no breach of Clause 22.2 was ruled.

The Panel noted its rulings above and subsequently ruled no breach of Clauses 9.1 and 2.

**APPEAL BY THE COMPLAINANT**

The complainant submitted a number of detailed comments, attachments and enclosures from a variety of sources including the National Institute for Health and Clinical Excellence (NICE) and the MHRA in support of her appeal. The complainant provided a copy of the Drug Analysis Print (DAP) for Champix which listed spontaneously reported adverse events. The complainant later stated that these submissions were only sent as they supported her final report provided as her final comments (see below).

**RESPONSE FROM PFIZER**

Pfizer submitted that whilst it had sympathy for the complainant's concerns it did not believe that it had breached the Code and therefore it agreed with the Panel's ruling.

Pfizer submitted that its materials for health professionals and patients responsibly described the safety profile of Champix, including any specific special warnings and precautions. The safety information was accurate and balanced and was

consistent with the SPC. Pfizer assured the Appeal Board that any safety changes to the SPC were always reflected rapidly in its materials for health professionals and patients. It was clearly important that the most up-to-date information was provided, and that it was based on the SPC.

Pfizer considered that in its response to the complaint and to the appeal, it had addressed any matters related to the Code.

**FINAL COMMENTS FROM THE COMPLAINANT**

The complainant stated that patients with neuropsychiatric disorders had a typically two to four-fold higher chance of being a smoker. Studies conducted in a variety of neuropsychiatric populations (eg attention-deficit hyperactivity disorder (ADHD), epilepsy, Alzheimer's, schizophrenia, Parkinson's) had collectively suggested that nicotine, was efficacious in remediating selected cognitive deficits associated with these disorders, thus providing a framework for understanding the specific vulnerability of these patients to smoking initiation and maintenance. However, the specific gain in cognitive performance produced by nicotine administration in healthy subjects with normal cognitive function was less clear. This submission reviewed the current understanding of central nicotinic acetylcholine receptors (nAChRs) systems in normal and neuropsychiatric disease states and, specifically, their role with respect to cognitive dysfunction and clinical symptoms in several specific neuropsychiatric populations, including ADHD, Alzheimer's, Parkinson's disease, Tourette's disorder, schizophrenia and affective disorders.

The complainant stated that mice which lacked the dopamine (DA) transporter (DAT) gene exhibited a phenotype reminiscent of schizophrenia and ADHD, which were alleviated by antipsychotic agents.

The complainant stated that alteration of nicotinic neurotransmission in DAT knockout (KO) mice showed that constitutively hyper dopaminergic (DAergic) DAT KO mice exhibited modifications in nicotinic receptor density in an area and subtype-dependent manner. In some DAergic areas, the small decrease in the Beta2* nicotinic subunit (nAChR) density contrasted with higher decrease and increase in the Alpha6* and Alpha7* nAChR densities, respectively.

Mutant mice were hypersensitive to the stimulant locomotor effects of nicotine at low doses, probably due to enhanced nicotine-induced extracellular DA level. They also showed hypersensitivity to the hypolocomotion induced by nicotine. In contrast, no hypersensitivity was observed for other nicotine-induced behavioral effects, such as anxiety or motor activity. Co-administration of nicotinic agonists at sub-active doses elicited opposite locomotor effects in wild-type and DAT KO mice.
These findings showed that a targeted increase of DA tone could be responsible for significant adaptations of the cholinergic/nicotinic neurotransmission. This study provided potential leads for the use of nicotine or combined nicotinic agonists to treat psychiatric disorders.

The complainant noted an article titled 'Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders' by Sacco *et al* (2004). The complainant further noted that Pfizer had stated that Champix had not been tested in these people. In the complainant's view it clearly had, as the papers looked at mentioned Champix, and all the papers' dates were before recommendations for Champix to be used as first-line treatment by NICE, for use on UK NHS. Also, one of Pfizer's scientists had the patent for the nicotinic receptors as he created the genetically altered mutated mice. He bred them and supplied them to Pfizer for medicine development looking at treatments for ADHD, Alzheimer's, epilepsy and other diseases that were triggered by mutations of nAChRs on withdrawal of Champix. His special mice had been purposely bred to have the Alpha4 mutation.

The complainant stated that the Alpha4 mutation was the one linked to epilepsy and Alpha7 and was linked to Alzheimer's and heart problems. Beta4 was linked to Parkinson's. The complainant stated that she could see the rational of design of potent medicines with selective binding properties but there were still many unanswered questions about these synthetic compounds.

The complainant stated that in her opinion too many were given out by the NHS just for stopping smoking in the general population. If it was used as second-line treatment for example in people who were showing symptoms of early COPD due to years of smoking or even lung cancer, with proper medical supervision, and a weaning off programme, then for these areas of the population it might be worth the risk as it could up their survival as it did stop you smoking while on the medicine.

The complainant stated that Pfizer must have known that withdrawal of Champix could trigger seizures and any of the above mentioned in 10% or more of the general population, as all nAChRs, dual inhibitors had very similar application.

5-HTa4+a7 association with Epilepsy. (Epilepsia, 2006 and Heterocyles, 2006).

The complainant stated that the 5-HTa4+a7 haplotype was associated with epilepsy type disorders, of which there were over 50 different types. Extracellular concentrations of norepinephrine and dopamine in the prefrontal cortex could triggered ADNFLE. Antagonist Champix made norepinephrine efflux greater than other compounds alone. Norepinephrine reuptake inhibitors were used for depression, ADHD and epilepsy.

Dopaminergic polymorphisms and regulatory problems in infancy. (Zeitschrift fur Kinder-und Jugendpsychiatrie and Psychotherpie, 2007).

The complainant stated that the presence of certain alleles in polymorphisms of the dopamine receptor gene (DRD4) and the dopamine transporter gene

(DAT1) increased a child's risk of developing ADHD or another mental disorder and effected girls slightly more than boys.

The complainant stated that this showed that smoking whilst pregnant could cause the polymorphisms before you were born, but until triggered by medicines that artificially stimulated DAT1 like Champix did. Withdrawal could trigger diseases as previously mentioned. And also as stated before, these papers showed, nicotine was therapeutic and vital in some people with any history of mental illness or seizures, who carried mutations of this nature. NRT would not have triggered epilepsy in the complainant, or others on withdrawal. This only happened from artificial stimulation of nAChRs, from Champix. There was no warning of any of this in any Pfizer prescribing monograph or SPC for GPs, NICE or the MHRA. It had been estimated that at least 20% of patients with epilepsy might present with features of ADHD (Tan and Appleton, 2005).

The incidence of first provoked and unprovoked seizure in patients with and without psychiatric diagnoses (Epilepsia, 2007 and Indian Pediatrics, 2005).

The complainant noted that the authors concluded that the results of this study were consistent with previous reports showing that patients with psychiatric disorders had a higher incidence rate of seizures than the general population.

Linkage disequilibrium which might point towards co-segregation of two polymorphisms was showing in population more often than expected.

DAT1 gene effects

The complainant stated that DAT1 gene effects in the striatum were involved in translating the genetic risk of ADHD. DAT1 genotype would affect brain activation patterns in a manner similar to that of stimulant medication, eg nicotine.

Management of access to branded psychotropic medications in private health plans (Clinical Therapeutics, 2007).

The complainant noted private plans were managing psychotropic costs using co-payment incentives rather than administrating controls. This approach was less intrusive for clinicians, but resulting higher co-payments could worsen already high rates of nonadherence.

Statement by NICE (August 2012).

The complainant stated that NICE had told patients they should sue health authorities if they denied them medicines deemed cost-effective for NHS. The complainant stated that cost-effective did not mean a medicine was safe to use, it was down to doctors to decide if a medicine was safe for most of their patients who they had available to them their medical history, to help make that prognosis not the head of NICE who did not have medical training to do so. This was proof that the government put profit before peoples' health; the price of medication should not come into it, full stop.

**APPEAL BOARD RULING**

The Appeal Board considered that patient safety was extremely important. The Appeal Board noted that this was a highly personal and important issue for the complainant and it did not doubt her sincerity on the matter. The complainant had submitted a large volume of information and had referred to the conduct of other organisations. The Appeal Board noted that the complainant stated in response to a question at the appeal that she had sent all of her documents in this case to the MHRA. The Appeal Board noted that its only role was to consider matters in relation to the requirements of the Code and specifically the Panel's rulings of no breach of Clauses 2, 7.9, 9.1, and 22.2. As stated in the introduction to the PMCPA Constitution and Procedure, the complainant had the burden of proving their complaint on the balance of probabilities.

The Appeal Board examined two documents which were current when the complainant was prescribed Champix. The Champix SPC (reviewed 26 April 2007) stated in Section 4.4, Special warnings and precautions for use, that there was no clinical experience with Champix in patients with epilepsy. Section 4.8 of the same SPC, Undesirable effects, did not refer to seizures, epilepsy or fits. The Appeal Board noted that the SPC and the PIL were regulatory documents and their contents were agreed with the regulators, the MHRA and the EMA. The PIL was based on the agreed SPC. The Pfizer leaflet entitled 'Information for patients who have been prescribed Champix (varenicline tartrate)' (ref SCE055, prepared November 2007) had to reflect the SPC and PIL and not be inconsistent with those regulatory documents. The Appeal Board noted that the Pfizer leaflet similarly did not refer to seizures, epilepsy or fits in the section headed 'What side effects might I experience'. The Pfizer leaflet did not state that there was no clinical experience with Champix in patients with epilepsy; the Appeal Board, however, did not consider that the Pfizer leaflet was inconsistent with the SPC in that regard.

The Appeal Board noted that the current Champix SPC did not refer to seizures, epilepsy or fits as possible adverse effects and so similarly neither did the current PIL.

The Appeal Board noted that the complainant had provided the Drug Analysis Print (DAP) for Champix which listed spontaneously reported adverse events reported in the UK from 1 July 1963 to 18 December 2012. The report run date was 19 December 2012. The earliest reaction date was 26 December 2006. The document provided by the complainant stated that the report recorded where at least one suspected adverse drug reaction (ADR) report had been received that specified the product as a 'suspected drug' (ie suspected causal association with the reaction). It further stated that suspected ADR reports sent to the Yellow Card Scheme were called spontaneous reports.

In this regard the Appeal Board noted the section 'seizures and seizure disorders NEC [not elsewhere classified]' gave a combined total of 74 for convulsions, epilepsy, partial seizures and status epilepticus. Other sections of the DAP recorded 3 reports of petit mal epilepsy and 15 of grand mal convulsions. The Appeal Board noted that no evidence had been provided to show that this was more than might normally have occurred in the general population who had not taken Champix. The Appeal Board noted that the DAP did not breakdown the data and there was no record of the situation in January 2008 when the complainant took Champix. The Appeal Board noted that the listing of an adverse event in the DAP did not prove that it had been caused by Champix. It was a record that the adverse event had happened in a patient who at the same time was taking Champix and that it might be causally related.

The Appeal Board noted that it was the role of the relevant EU or UK regulatory authority to decide the wording of SPCs and PILs. The wording of an SPC was likely to change over time as experience with a medicine grew. In that regard the Appeal Board noted correspondence between the complainant and the MHRA and in particular an email from the MHRA dated 1 October 2012 which stated that cases of seizures and epilepsy reported for varenicline (Champix) would be reviewed within the European regulatory framework in the next couple of months. It was important that the MHRA was provided with all relevant information and the complainant stated to the Appeal Board that she had provided all of her documents to the MHRA. At the appeal hearing the Appeal Board queried the accuracy of some aspects of the material submitted by the complainant and the conclusions drawn.

The Appeal Board noted that the complainant had provided a copy of a leaflet prepared by Pfizer Canada Inc (last revised 14 December 2011). Under a heading 'Warnings and precautions' patients were advised not to engage in potentially hazardous tasks such as driving or operating machinery as some people had reported, among other things, blackouts and seizures. Such events, however, were not included in the section of the leaflet headed 'Side effects and what to do about them'. The US full prescribing information (revised December 2012) listed convulsion as a rare side effect. Neither the Canadian nor the US document specifically included the word 'epilepsy'. The Appeal Board also noted that the patient leaflet from Australia (dated February 2007) referred to seizures and fits. Pfizer had submitted that this leaflet was used in both Australia and New Zealand and that the New Zealand data sheet did not refer to seizures or fits. Pfizer had submitted that the reference to seizures and fits in the Australian/New Zealand document had been an error and had been removed in September 2007. The Appeal Board noted that the information provided by Pfizer in the UK reflected the information in the SPC and PIL which had been agreed with the UK regulatory authorities. The Appeal Board considered that it had not been provided with any evidence to show that the information Pfizer had provided to patients taking Champix in January 2008 when the complainant took Champix, was inconsistent with the evidence available at that time with regard to the possibility of developing epilepsy as a consequence of taking or stopping treatment with Champix. Therefore the failure to refer to seizures or fits in Pfizer produced patient leaflets for the UK available in January 2008 was not a failure to reflect the available evidence. Thus the Appeal Board upheld the Panel's ruling of no breach of Clause 7.9. The appeal on this point was unsuccessful.

Similarly the Appeal Board considered that it had not been provided with any evidence to show that information provided to the public by Pfizer in January 2008 was not factual or balanced with regard to the side-effect profile of Champix. Not referring to fits and seizures in Pfizer produced patient leaflets did not mean that this material was incorrect or unbalanced. Thus the Appeal Board upheld the Panel's ruling of no breach of Clause 22.2. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and consequently upheld the Panel's ruling of no breach Clauses 9.1 and 2. The appeal on this point was unsuccessful.

**Complaint received** **5 October 2012**

**Case completed** **6 March 2013**

**Post Appeal Board Meeting**

As this case involved an issue of patient safety, the Appeal Board requested that the following details be provided for information only. Please note that none of the information below was known when the case was considered and it would not have changed the Appeal Board's decision which was based on information available in 2008.

Following the appeal, the complainant provided an email from the MHRA dated 13 March 2013 which included:

> 'A review of seizures was conducted as part of the last Periodic Safety Update Report (PSUR) for Champix. The PSUR assessment was considered by the EU Pharmacovigilance Risk Assessment Committee (PRAC) at its meeting 26-29 November 2012. The minutes of this meeting, which included the outcome of the assessment of seizure-related events, are published on the EMA website …. PRAC recommended that the product information (SPC and PIL) be updated to include seizure-related events.'

The minutes from PRAC stated:

> 'Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Champix, a centrally authorised medicine containing varenicline, and issued a recommendation on its marketing authorisation.

**Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Champix (varenicline) in the approved indication(s) remains favourable.

- The PRAC recommended updating the product information with regard to seizure-related events. Therefore the current terms of the marketing authorisation should be varied …'

The updated SPC dated 11 March 2013 included in Section 4.4 special warnings and precautions for use, the following:

**Seizures**

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with CHAMPIX. CHAMPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Section 4.8 Undesirable effects listed seizures as an uncommon nervous system disorder.

The PIL had also been updated. The version on the eMC stated that the leaflet was last approved in 03/2013.

# EX-EMPLOYEE/DIRECTOR v ASTRAZENECA

## Presentation on Seroquel

**An ex-employee of AstraZeneca referred to Case AUTH/2297/1/10; in that case, he drew attention to a BBC Radio 4 programme in which he had stated that as a former medical adviser for Seroquel, he had been pressurised to approve promotional claims for the medicine which stated that weight gain was not a problem.**

**The complainant now referred to five presentations on the AstraZeneca website (www.astrazeneca.com) which he alleged made similar false claims to those at issue in Case AUTH/2297/1/10.**

**Alleged breaches of undertaking were taken up with the Director acting as the complainant as the PMCPA was responsible for ensuring compliance with undertakings.**

**The detailed response from AstraZeneca is given below.**

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

**The Panel noted that whilst the complainant referred to Case AUTH/2297/1/10 that case was considered and published alongside two closely similar cases, Cases AUTH/2294/1/10 and AUTH/2296/1/10. The rulings in these cases were interlinked and AstraZeneca had provided one undertaking in relation to all three. The Panel examined the previous rulings relating to claims about weight.**

**The Panel noted that AstraZeneca had provided the requisite undertaking and assurance for the previous cases in March 2010. The advertisement at issue then was last used in May 2004. Undertakings required the company concerned to cease use of the material in question and any similar material and give an assurance that all possible steps would be taken to avoid a similar breach of the Code in the future. In the Panel's view, if promotional material was originally at issue, an undertaking was not necessarily limited to closely similar claims solely in promotional material as inferred by AstraZeneca. Much would depend on the circumstances. The Panel noted that the presentations at issue, which AstraZeneca submitted were written for the international investor community, were available on www.astrazeneca.com. The Panel considered that in general, if an undertaking was given not to use a claim then the use of the same claim with a different audience was likely to be unacceptable under the Code, irrespective of whether it was in breach of the original undertaking.**

**On the information before it, the Panel saw no reason why material published on AstraZeneca's corporate website would not be subject to the UK Code.**

**It appeared from AstraZeneca UK's submission that the company had not examined the material now at issue when the undertaking was given in March 2010. The fact that AstraZeneca archived such presentations on its website for an indefinite period did not mean that if such material was in breach of the Code, it was somehow acceptable to keep it on the website. The Panel did not consider that either the need to change archiving policy for such presentations or the difficulty of finding the material on the website were relevant as to whether there had been a breach of undertaking.**

**The Panel noted that none of the presentations included the claim previously at issue 'The only atypical with placebo level EPS (including akathisia) and placebo level prolactin concentration and a favourable weight profile across the full dose range'.**

**The Panel then considered whether the claims in the presentations were sufficiently similar to the claim previously ruled in breach of the Code. The Panel considered that most of the claims relating to weight gain in the five presentations were sufficiently different from the claim previously at issue for them not to be caught by the undertaking. No breach of the Code was ruled.**

**However the Panel noted one slide headed 'Seroquel – strong differential advantage across the indications' included the claims 'placebo-like EPS', 'placebo-like prolactin levels', 'low incidence of sexual dysfunction' and 'weight-neutral in the long-term' which appeared beneath the subheading 'Unique tolerability profile' and above the claim 'Improvement without impairment'. The Panel considered that this slide related solely to the features of Seroquel and in effect claimed that it was the only atypical that was weight-neutral in the long-term. The Panel considered that this claim was sufficiently similar to a claim that only Seroquel had a favourable weight profile compared with other atypicals for it to be covered by the undertaking in the previous case. A breach of undertaking was ruled. The Panel ruled that high standards had not been maintained.**

**The Panel considered that failing to comply with the undertaking brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. The rulings were appealed by AstraZeneca.**

**The Appeal Board decided that the presentation came within the scope of the Code as it was information about, *inter alia*, a prescription only medicine Seroquel, which appeared on AstraZeneca's website. In that regard the age of the data was irrelevant. A potential investor in the company might look on AstraZeneca's website for information and find the presentation at issue.**

**The Appeal Board was concerned that AstraZeneca had not looked at archived material on its website in relation to the undertaking given in the previous cases. The Appeal Board noted AstraZeneca's submission that this was historical material. The Appeal Board further noted that the material was still in the public domain. There was no indication on the material itself that it was historical. The impression was that the material could still be current. The Appeal Board noted that an undertaking required that the promotional activity or use of the material in question and any similar material, if not already discontinued or no longer in use, would cease forthwith and that all possible steps would be taken to avoid a similar breach of the Code in the future. Details of certain actions taken by the company to implement the undertaking had to be provided, including the date on which the material was finally used or appeared and/or the last date on which the activity took place.**

**The Appeal Board noted AstraZeneca's submission that the presentation was clearly archived, no longer in use and not used proactively.**

**The Appeal Board noted that the slide was headed 'Seroquel – Strong differential advantage across the indications'. The Appeal Board noted that the first bullet point underneath the heading stated 'Broad-based efficacy' beneath which three sub-bullets stated 'as effective as other atypicals', 'efficacy in one week' and 'effective in the long-term'. The Appeal Board considered that together these three points contributed to the broad-based efficacy claim; each individual point on its own was not a claim for broad-based efficacy and would not be read as such. In the Appeal Board's view the lower half of the slide would be interpreted in the same way so that 'placebo-like EPS', 'placebo-like prolactin levels', 'low incidence of sexual dysfunction' and the claim at issue, 'weight-neutral in the long-term', would be seen to collectively contribute to Seroquel's 'Unique tolerability profile'. The Appeal Board did not consider that each point on its own would be read as a unique feature of Seroquel.**

**The Appeal Board noted that the undertaking given in Cases AUTH/2294/1/10, AUTH/2296/1/10 and AUTH/2297/1/10 related to the claim, 'The only atypical with placebo level EPS (including akathisia) and placebo level prolactin concentrations and a favourable weight profile across the full dose range'.**

**The Appeal Board considered that the presentation of the claim 'weight-neutral in the long-term' as one of four bullet points beneath the heading 'Unique tolerability profile' in the material at issue was such that it was not sufficiently similar to the claim previously at issue for it to be covered by the undertaking. Taking all the circumstances into account, the Appeal Board ruled no breach of the Code including Clause 2. The appeal was successful.**

An ex-employee of AstraZeneca referred to his previous complaint about the promotion of Seroquel by AstraZeneca, Case AUTH/2297/1/10. In that case, he drew attention to a BBC Radio 4 programme in which he had stated that as a former medical adviser for Seroquel, he had been pressurised to approve promotional claims for the medicine which stated that weight gain was not a problem.

The report for Case AUTH/2297/1/10 had been published in conjunction with two related cases, Cases AUTH/2294/1/10 and AUTH/2296/1/10.

**COMPLAINT**

The complainant referred to five presentations on the AstraZeneca website (www.astrazeneca.com) which he alleged made similar false claims to those at issue in Case AUTH/2297/1/10.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 9.1 and 25.

Alleged breaches of undertaking were taken up with the Director acting as the complainant as the PMCPA was responsible for ensuring compliance with undertakings.

**RESPONSE**

AstraZeneca refuted the implied allegation that it had breached Clause 25 by failing to comply with undertakings to the Authority provided upon conclusion of a previous complaint that originated amongst others from the same complainant.

The presentations in question were written for international investors interested in AstraZeneca. As such, they were presented by senior AstraZeneca executives at business review meetings and in one case a research and development (R&D) update day. Full details were provided.

Due to the global audience, the presentations originated from AstraZeneca's global commercial and R&D teams. As they were not of promotional intent, in line with the requirements of the Code, they had not been certified. The presentations would have been reviewed and agreed at a corporate level in accordance with AstraZeneca process for information that reflected forward looking statements of interest to international investors.

AstraZeneca's current policy was to archive analyst and other business related presentations on its website for an indefinite period, in the spirit of making this information available to those who were unable to participate in the live events as well as for historical reference. Their removal would need to be made in consultation with AstraZeneca's Disclosure Committee as it would reflect a more general change of archiving practice for investor related presentations.

No specific group was directed to this content.

The links provided by the complainant were to presentations on AstraZeneca's corporate website. However, AstraZeneca noted the following in relation to the accessibility of the presentations:

- searching the links themselves in Google did not deliver any results because the documents had not been tagged in line with there being no intent to make these easily accessible or widely available to non-interested parties
- it was not possible to identify the web source of these documents for similar reasons above
- in order to find the documents one would have to specifically look for them. Even with prior knowledge, to get to them from the homepage of the corporate website needed at least 4 clicks. The likelihood of finding the documents when starting from a search engine like Google was very low.

AstraZeneca submitted that it was likely that, in order to access the documents, the complainant and others with a specific interest would have spent a considerable amount of time searching the archive, making it unlikely that a casual visitor to the corporate website would inappropriately stumble upon them.

AstraZeneca did not believe that the weight change claims in these presentations fell within the scope of the previous ruling insofar as these presentations were historical, non-promotional records that were not directed at health professionals. It was also clear from the chronology of the presentations that AstraZeneca's statements in relation to weight and Seroquel evolved as a balanced and fair reflection of the evidence available at the time:

- 1999 – minimal weight gain
- 2001 – weight-neutral in the long-term
- 2004 – favourable weight profile long-term
- 2006 – less weight gain than with olanzapine.

AstraZeneca submitted that the weight related claims previously ruled in breach were fully addressed when Case AUTH/2297/1/10 was considered. The claim related to a 2004 advertisement and when the undertaking was signed in 2010, AstraZeneca was, and remained, confident that the claim at issue did not form any aspect of Seroquel marketing in the UK and had not done so for some considerable time. As such AstraZeneca stated that it would not revisit the details including the data.

In conclusion, AstraZeneca denied any breaches of Clauses 2, 9.1 and 25.

AstraZeneca was asked by the Panel to respond to the case preparation manager's request for information about what action the company took following the outcome of the previous cases to ensure that all of the claims at issue, and any similar claims, were withdrawn.

AstraZeneca stated that its response to the cases in 2010 was in the context of the claims in question being of a historical nature that had ceased to be used in any UK promotional materials.

AstraZeneca submitted that the actions taken by the UK Seroquel team following the 2010 rulings were proportionate to the nature of the material found to be in breach, in that the UK Seroquel team reviewed all of the current promotional materials for the product. As the weight related claims, or similar, had long since ceased to be used, no such materials were required to be recalled as no promotional material carried such claims.

Weight related claims ceased to be used in UK promotional materials as set out and supported by the Seroquel Current Claims Document (CCD). This was an AstraZeneca confidential document for internal use only, which captured the claims approved for use as well as any undertakings and/or other decisions not to use certain claims (pages 2 and 3 specifically took into account the ABPI and inter-company undertakings). No CCD after 2007 included weight related comparisons with other treatments and the 2008 CCD was provided to support AstraZeneca's position in this regard.

AstraZeneca restated its position that the presentations in question did not fall within the scope of the previous rulings or the Code insofar as they were corporate historical records intended for the investor community; they were non-promotional and were not directed at health professionals.

AstraZeneca denied the allegation that it had breached undertakings made in relation to Case AUTH/2294/1/10 and any breaches of Clauses 25, 9.1 or 2 or at all.

**PANEL RULING**

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

The Panel noted that whilst the complainant referred to Case AUTH/2297/1/10 that case was considered and published alongside two closely similar cases, Cases AUTH/2294/1/10 and AUTH/2296/1/10. The rulings in these cases were interlinked and AstraZeneca had provided one undertaking in relation to all three.

The Panel examined the three previous rulings relating to claims about weight.

**Case AUTH/2294/1/10**

The Panel noted that the Seroquel advertisement at issue, published in the British Journal of Psychiatry, April 2004, featured the claim 'The only atypical with placebo level EPS [extra-pyramidal symptoms] (including akathisia) and placebo level prolactin concentrations and a favourable weight profile across the full dose range'. The Panel thus considered that the claim in full sought to establish Seroquel as an atypical antipsychotic which was distinctly different to the others in the class in that it was the only one to have

placebo level EPS, placebo level prolactin concentrations and a favourable weight profile across the full range.

The Panel noted that in the absence of any explanation it was left to the readers' judgement as to what was meant by a 'favourable weight profile'. The Panel noted that Allison *et al* (1999) had estimated and compared the effects of antipsychotics (both conventional and atypical) on bodyweight. The authors concluded that all of the antipsychotics examined were associated with weight gain. Among the atypical agents the mean increases in weight were 4.55kg (clozapine), 4.15kg (olanzapine), 2.92kg (sertindole), 2.1kg (risperidone) and 0.04kg (ziprasidone). The mean increase in weight with Seroquel was not calculated due to lack of data.

The Panel considered that if all of the other atypical antipsychotics were known to cause weight gain then it was not unreasonable for readers to assume that if Seroquel was 'The only atypical with … a favourable weight profile across the full dose range' then it might be an atypical with no effect on bodyweight. This was not so. Arvanitis and Rak (1997) reported that the mean increase in weight was 2.2kg (n=1085). Allison *et al* had reported that the mean increase in weight for risperidone was 2.1kg and 2.92kg for sertindole. Across the dose range for Seroquel, 75/150/300/600/750mg daily, the mean increase in weight was 0.9/2.9/2.0/2.6/2.3kg respectively. Jones and Huizar (2003) reported a mean increase in weight of 1.8kg with Seroquel therapy. Brecher *et al* (2000) reported on the long-term weight changes in 427 patients over 18 months. Weight change differed over time from -1.53kg after weeks 40-52 (n=41) to +1.94kg after weeks 53-78.

The Panel noted that the relevant Seroquel SPC (October 2003) listed weight gain as a common (≥1% - <10%) adverse event which occurred predominantly during the early weeks of therapy.

Overall the Panel considered that the advertisement was misleading with regard to the effect on bodyweight that would be expected to be observed with Seroquel therapy compared with the other atypical medicines. Although the advertisement did not state 'no weight gain' as alleged it sought to differentiate Seroquel from other medicines in the class in that it was the only one with a 'favourable weight profile across the full dose range'. Given that the other medicines caused weight gain, the advertisement could be read as implying that Seroquel did not. This was not so. Similarly, the advertisement could be read as implying that Seroquel had a clear advantage regarding its 'favourable weight profile …' and this was not supported by the data submitted by AstraZeneca. The claim 'The only atypical with … a favourable weight profile…' was thus misleading and could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. The Panel considered that the claim did not reflect the evidence regarding the side-effect of weight gain. A breach of Clause 7.9 of the Code was ruled.

**Case AUTH/2296/1/10**

The complainant referred to an online news item which referred to the advertisement at issue in Case AUTH/2294/1/10.

The Panel considered that its rulings in Case AUTH/2294/1/10 of breaches of Clauses 7.2, 7.4 and 7.9 applied here also. The Panel further considered that, given the data, high standards had not been maintained. A breach of Clause 9.1 was ruled.

Misleading prescribers about a potential side-effect of therapy could prejudice patient safety and this was referred to in the supplementary information to Clause 2 as an example of an activity likely to be in breach of that clause. On balance, however, the Panel considered that the circumstances were not such as to warrant a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

**Case AUTH/2297/1/10**

This case concerned, *inter alia*, the same advertisement at issue in Case AUTH/2294/1/10.

The Panel considered that its rulings above in Cases AUTH/2294/1/10 and AUTH/2296/1/10 applied here also.

The complainant in this case appealed the Panel's ruling of no breach of Clause 2.

The Appeal Board noted that between 1997 and 2004 there was increasing evidence that weight gain was an issue with Seroquel. Spielmans and Parry reported that in July 2008 an internal analysis of quetiapine studies in schizophrenia conducted from 1993-1999, concluded that 'the incidence rate in adult patients with weight gain ≥7% in all trials was 18.2%'. In the 2004 SPC weight gain was listed as a common (≥1% - <10%) adverse event; in the 2009 SPC it was listed as a very common (>10%) event. There was also data to show that in terms of the amount of weight gained, Seroquel was no different to some other atypical antipsychotics. The Appeal Board was concerned that the claim 'The only atypical with placebo level EPS [extra-pyramidal symptoms] (including akathisia) and placebo level prolactin concentrations and a favourable weight profile across the full dose range' had favoured Seroquel in terms of its weight gain profile vs other atypical antipsychotics yet the evidence had not supported this.

The Appeal Board was concerned about the lack of information provided by AstraZeneca about the generation of the advertisement at issue. It was also extremely concerned about email trails which implied that the company was keen not to disclose certain data. However, the Appeal Board noted that it was limited to making its decision based on activity in the UK and in that regard the advertisement at issue was the only one that had been specifically identified. The Appeal Board noted the Panel's ruling of breaches of the Code which had been accepted by AstraZeneca. The Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 and so it upheld the Panel's ruling of no breach of that clause. The appeal was thus unsuccessful.

**Case AUTH/2538/10/12**

Turning to the present case, Case AUTH/2538/10/12, the Panel noted that AstraZeneca had provided the requisite undertaking and assurance for the previous

cases on 12 March 2010. The advertisement at issue in those cases was last used in May 2004. An undertaking required a company to cease use of the material in question and any similar material and give an assurance that all possible steps would be taken to avoid a similar breach of the Code in the future. In the Panel's view, if the material originally at issue was a claim in promotional material, an undertaking was not necessarily limited to closely similar claims solely in promotional material as inferred by AstraZeneca. Much would depend on the circumstances. The Panel noted that the presentations at issue were available on www.astrazeneca.com. AstraZeneca submitted that the presentations were written for the international investor community. The Panel considered that in general, if an undertaking was given not to use a claim then the use of the same claim with a different audience was likely to be unacceptable under the Code, irrespective of whether it was in breach of the original undertaking.

Firstly, the Panel had to consider whether the material came within the scope of the Code as it was placed on the corporate (astrazeneca.com) website. The Panel noted that there was no submission from the company specifically on this point, however, AstraZeneca was a UK company and thus its activities and materials, those of any UK based affiliate and other activities taking place in the UK organised by an overseas affiliate all had to comply with the Code. The Panel noted that AstraZeneca's corporate headquarters were based in the UK. On the information before it, the Panel saw no reason why material published on the corporate website would not be subject to the UK Code.

It appeared from AstraZeneca UK's submission that the company had not examined the material now at issue when the company had given its undertaking in March 2010. The fact that AstraZeneca archived such analyst and business related presentations on its website for an indefinite period did not mean that if such material was in breach of the Code, it was somehow acceptable to keep it on the website. The Panel did not consider that the need to change archiving policy for such presentations was relevant as to whether or not there had been a breach of undertaking. Similarly, the Panel did not accept AstraZeneca's submission that the difficulty of finding the material on the website was relevant as to whether or not there had been a breach of undertaking.

The Panel examined each presentation separately and each of the slide sets referring to weight. None of the slides included the claim previously at issue 'The only atypical with placebo level EPS (including akathisia) and placebo level prolactin concentration and a favourable weight profile across the full dose range'.

The Panel considered whether the claims in the presentations were sufficiently similar to the claim previously ruled in breach of the Code.

**1 Seroquel Presentation 2004**

This presentation included two slides headed 'The ideal schizophrenia treatment' and 'The ideal bipolar mania treatment'. Each compared Seroquel, risperidone, olanzapine and aripiprazole for certain features including 'Favourable weight profile long-term'. On each slide there was a cross for olanzapine for this feature and ticks for the other three products indicating that olanzapine was the only one of these medicines which did not have a favourable weight profile long-term.

The Panel did not consider that either of these two slides in effect claimed that Seroquel was the only medicine with a favourable weight profile. The slides were not sufficiently similar for them to be covered by the previous undertaking. No breach of Clause 25 was ruled and consequently no breach of Clauses 9.1 and 2. These rulings were not appealed.

During the consideration of this aspect of the case the Panel was concerned that the title of the slides implied that Seroquel was the ideal treatment and queried whether this was consistent with the requirements of Clause 7.10. The Panel requested that AstraZeneca be advised of its concerns.

**2 Seroquel Presentation 2006**

This presentation included two slides headed 'Seroquel physician perceptions: Schizophrenia' and 'Seroquel physician perception: Bipolar' which stated under the bullet point 'Superior tolerability' three further bullet points, 'Low rate of EPS (inc.akathisia)', 'Low rate of prolactin induction' and 'Less weight gain than with olanzapine'. The slide concluded that Seroquel had an overall favourable benefit/risk profile.

Again, the Panel did not consider that the claim 'Less weight gain than with olanzapine' in effect claimed that Seroquel was the only medicine with a favourable weight profile. The claim was not sufficiently similar for it to be covered by the previous undertaking. No breach of Clause 25 was ruled and consequently no breach of Clauses 9.1 and 2. These rulings were not appealed.

**3 AstraZeneca Presentation 1999**

This presentation included a slide headed 'Seroquel – minimal weight gain' beneath which appeared data showing weight gain for Seroquel, presented as a bar chart, and for olanzapine, presented as a graph.

The Panel did not consider that the claim 'Seroquel – minimal weight gain' in effect claimed that Seroquel was the only medicine with a favourable weight profile. The claim was not sufficiently similar for it to be covered by the previous undertaking. No breach of Clause 25 was ruled and consequently no breach of Clauses 9.1 and 2. These rulings were not appealed.

**4 Development Portfolio Review Presentation 2002**

This presentation included two slides, one headed 'Seroquel Improvement without impairment' which compared a number of features for risperidone, olanzapine, ziprasidone, aripiprazole and Seroquel including 'Weight-neutral long-term'. There was a tick for Seroquel, ziprasidone and aripiprazole and a cross for olanzapine and risperidone.

The Panel did not consider that the claim that Seroquel, ziprasidone and aripiprazole were 'Weight-neutral long-term' was sufficiently similar to the previous claim that Seroquel was the only medicine with a favourable weight profile for it to be covered by the previous undertaking. No breach of Clause 25 was ruled and consequently no breach of Clauses 9.1 and 2. These rulings were not appealed.

A second slide headed 'Seroquel – strong differential advantage across the indications' included the claims 'placebo-like EPS', 'placebo-like prolactin levels', 'low incidence of sexual dysfunction' and 'weight-neutral in the long-term' which appeared beneath the subheading 'Unique tolerability profile' and above the claim 'Improvement without impairment'.

The Panel considered that this slide related solely to the features of Seroquel and in effect claimed that it had an advantage in that it was the only atypical that was weight-neutral in the long-term. This appeared to be inconsistent with the first slide referred to above. The Panel queried which of these claims was accurate. However, it only considered whether there had been a breach of undertaking. The Panel considered that to claim that Seroquel was the only atypical that was weight-neutral was sufficiently similar to a claim that only Seroquel had a favourable weight profile compared with other atypicals for it to be covered by the undertaking in the previous case. A breach of Clause 25 was ruled. The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. These rulings were appealed by AstraZeneca.

Failing to comply with an undertaking and assurance was cited as an example of an activity likely to be in breach of Clause 2. The Panel considered that failing to comply with the undertaking brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed by AstraZeneca.

**5 AstraZeneca Portfolio Presentation 2001**

This presentation included a slide headed 'Seroquel substainable benefits in $7 billion market' which again compared certain features of Seroquel, olanzapine, risperidone and ziprasidone including 'weight neutral in the long term' which was listed as a positive feature for Seroquel and ziprasidone.

The Panel did not consider that this slide in effect claimed that Seroquel was the only one of these medicines with a favourable weight profile. The slide was not sufficiently similar for it to be covered by the previous undertaking. No breach of Clause 25 was ruled and consequently no breach of Clauses 9.1 and 2. These rulings were not appealed.

During its consideration of this case, the Panel was concerned that AstraZeneca UK had apparently interpreted the undertaking so narrowly. Further, the Panel considered that the local company, in this instance AstraZeneca UK, needed to ensure that relevant rulings, including those relating to the acceptability of clinical claims, were disseminated so that corporate claims and activities used in the UK could be reviewed if appropriate.

**APPEAL FROM ASTRAZENECA**

AstraZeneca submitted that the undertaking at issue related to the following claim for Seroquel: 'The only atypical with placebo level EPS (including akathisia) and placebo level prolactin concentrations and a favourable weight profile across the full dosage range'. In the previous cases (Journalist, Member of the public and Ex-employee v AstraZeneca - Cases AUTH/2294/1/10, AUTH/2296/1/10 and AUTH/2297/1/10), the Panel ruled that the claim misleadingly implied that Seroquel was the only atypical with a favourable weight profile. Accordingly, it was not disputed that, as a consequence of its undertaking, AstraZeneca was not entitled to claim or imply that Seroquel was the only atypical with a favourable weight profile.

In the present case, Case AUTH/2538/10/12, the Panel analysed five slide presentations in order to assess whether AstraZeneca had implied that Seroquel was the only atypical with a favourable weight profile (the Panel acknowledged that the identical claim was not used). These slide presentations were held in the archived material for investors on AstraZeneca's website (www.astrazeneca.com). In just one of the five presentations, entitled 'Development Portfolio Review' the Panel considered that the weight claim was 'similar' to the prohibited claim. Specifically, the Panel concluded that the presentation effectively stated that Seroquel was the only atypical that was weight-neutral in the long-term, and that it therefore fell within the scope of the undertaking (the term 'weight-neutral' was, in the Panel's estimation, equivalent to 'favourable weight profile').

AstraZeneca strongly contested the Panel's interpretation of the claim at issue. Specifically, the Panel had misconstrued the claim: AstraZeneca had not presented Seroquel as the only atypical that was weight-neutral; Seroquel was presented as unique as regards the totality of its advantages. For this reason, AstraZeneca refuted the ruling of breach of Clause 25. However, even if the Appeal Board disagreed with AstraZeneca's interpretation and upheld the ruling of a breach of Clause 25, it submitted that all the circumstances of the case could not support a ruling of a breach of Clause 9.1, let alone a ruling of a breach of Clause 2. Before setting out AstraZeneca's grounds for appeal in relation to each of the clauses at stake, it was important to recall these circumstances, namely: the context of the present complaint, and the nature of the material at issue.

AstraZeneca submitted that the 2002 presentation was aimed at an international investor audience, and was developed as an integral part of the annual business review process. As such it did not focus solely on Seroquel but covered other areas of interest to investors. Along with other analyst and business related presentations, this presentation was maintained on AstraZeneca's corporate website as a historical record. These presentations were not promotional in

either intent or effect: they had short-term relevance for the international investor audience from the business review perspective, but beyond that they were not actively disseminated and were of interest only to someone actively seeking historical information. In fact, the presentation in question was of interest only to a vexatious complainant who had a particular agenda and who knew what he was looking for. This was supported by the fact that the presentation was:

- historic material from 2002
- not proactively distributed
- not tagged and therefore very difficult to find via an internet search engine without prior specific knowldege of the presentation contents
- held in a website archive
- difficult to find within the website itself (at least four clicks were needed to get to this content from the homepage).

AstraZeneca submitted that in the circumstances, the Panel's ruling was disproportionate and unfounded. Even if the weight claim in the presentation fell within the scope of the undertaking (which AstraZeneca strongly refuted), the alleged breach was not such as to bring discredit upon or reduce confidence in the industry; such a conclusion was not consistent with what the Code tried to achieve. AstraZeneca noted that this was not the 'typical' breach of undertaking case where a particular claim was ruled in breach of the Code was used again in the future (in some cases due to the company's error, in other cases due to the action of agents/publishers). Rather, this complaint arose as a consequence of a vexatious ex-employee who wanted to find fault with the company; the Code should not be the forum for such conduct.

AstraZeneca noted the Panel was concerned in relation to the company's interpretation of the undertaking given in Cases AUTH/2294/1/10, AUTH/2296/1/10 and AUTH/2297/1/10. AstraZeneca emphasised that it took all regulatory matters seriously and that the actions it took when it provided the undertaking were thorough and proportionate in the circumstances.

AstraZeneca refuted the Panel's ruling of a breach of Clause 25 and submitted that the Panel had misconstrued the weight claim in the presentation. When properly construed, AstraZeneca submitted that the claim did not fall within the scope of the undertaking.

AstraZeneca submitted that it was important first to summarise the content of the two slides within the Seroquel section of the presentation which referred to weight. The two slides should be considered in the context of each other and the flow of the entire presentation (an individual slide was clearly not intended to be presented or viewed in isolation).

The Panel considered two slides, both of which contained statements about Seroquel with regard to weight. The first slide (slide 13) headed 'Seroquel Improvement without Impairment' compared several features for risperidone, olanzapine, ziprasidone, aripiprazole and Seroquel and, through the use of ticks and crosses, explained that Seroquel, ziprasidone and aripiprazole were weight-neutral long-term (whereas the others were not). As slide 13 did not claim or imply that Seroquel was the only medicine with a favourable weight profile, the Panel concluded that this claim did not fall within the scope of the undertaking and therefore ruled no breach. AstraZeneca agreed with this analysis. However, the Panel objected to slide 18 which was headed 'Seroquel – Strong differential advantage across the indications' and contained the following bullet and sub-bullets:

- 'Unique tolerability profile
  - placebo-like EPS
  - placebo-like prolactin levels
  - low incidence of sexual dysfunction
  - weight-neutral in the long-term.'

According to the Panel, 'this slide related solely to the features of Seroquel and in effect claimed that it had an advantage in that it was the only atypical that was weight-neutral in the long-term'. The Panel thus interpreted the word 'unique' as relating to each of the four qualities individually, and it concluded that the claim that Seroquel was unique in being weight-neutral was sufficiently similar to the claim that only Seroquel had a favourable weight profile such that it fell within the scope of the undertaking. Based on its interpretation, the Panel noted that it considered the claim to be inconsistent with the claim made in slide 13 that Seroquel was one of three, out of five products, which were weight-neutral in the long-term.

AstraZeneca submitted that the Panel's interpretation of slide 18 was not justified when considered in the proper context of the presentation as a whole; nor was it justified on the basis of the intended or manifest meaning of slide 18 when considered in isolation. When properly interpreted, it might be seen that the claim in slide 18 did not fall within the scope of the undertaking, and further that there was no inconsistency between slides 13 and 18.

AstraZeneca submitted that, when read in the context of slide 13 and the presentation as a whole, slide 18 could not be interpreted as claiming that Seroquel was the only atypical that was weight-neutral in the long-term. Indeed, slide 13 set the scene by comparing Seroquel with other atypical antipsychotics against specific criteria one of which was 'weight-neutral long-term'. Therefore, as the Panel acknowledged, slide 13 made it clear that Seroquel was one of three atypical antipsychotics that were 'weight-neutral long-term'. AstraZeneca submitted that it was within this context that slide 18 detailed the qualities of Seroquel. The intended and manifest meaning of the slide was to present a unique overall tolerability profile made up of four factors; there was no suggestion that Seroquel was unique in respect of each or any single characteristic assessed separately. This was consistent with slide 13 which presented Seroquel as having a unique profile overall – as it was the only product with ticks in each category. Indeed, it was inconceivable that readers would interpret slide 18 to mean that Seroquel was unique in being weight-neutral in the long-term; rather, the slide would be interpreted in the context of slide 13, which showed that Seroquel was one of three atypical antipsychotics having this particular characteristic.

AstraZeneca submitted that this was also supported by the wording at the bottom of slide 18 – 'Improvement without Impairment' – which directly echoed the title of slide 13, 'Seroquel Improvement without Impairment'. Accordingly, the two slides were not inconsistent with one another as the Panel claimed; AstraZeneca submitted that they were fully consistent as the first presented an overview of Seroquel's benefits as against its competitors, and the second focused on the specific benefits of Seroquel. The slides therefore followed a logical and coherent order and were intended to be read in their entirety. Finally, on this point, the presentation in question could only be downloaded as a PDF, and not as a PowerPoint file, so the two slides could not be separated from one another. This underscored AstraZeneca's position that the slide ruled in breach could not and should not be considered independently and out of context of the whole presentation.

AstraZeneca submitted that even when considered in isolation, slide 18 did not make any claim that each individual element of the profile was unique. Rather, it was the combination of the four factors listed which together constituted a 'Unique tolerability profile'. This meaning was also achieved visually through the structure of the statement, namely the use of a main bullet ('Unique tolerability profile') followed by sub-bullets detailing the four factors of that profile as noted above. There was no suggestion that any factor, taken in isolation, would result in a 'unique' tolerability profile.

Accordingly, contrary to the Panel's ruling, AstraZeneca submitted that the content of slide 18 could not be construed as a claim that Seroquel was the only atypical that was weight-neutral in the long-term; the uniqueness of Seroquel related to the totality of its advantages.

On the basis of the above, AstraZeneca submitted that it had not breached its undertaking by retaining the presentation on its website, and that there was therefore no breach of Clause 25.

AstraZeneca submitted that the Panel's ruling of a breach of Clauses 9.1 and 2 were based on the ruling of a breach of Clause 25, which AstraZeneca refuted. As such, for the reasons stated above, the ruling of breaches of Clauses 2 and 9.1 automatically fell away.

However, even if the Appeal Board did not agree with AstraZeneca regarding the meaning of slide 18 and ruled a breach of Clause 25, AstraZeneca submitted that it had not, in any event, failed to maintain high standards (Clause 9.1) or brought discredit upon and reduced confidence in the pharmaceutical industry (Clause 2).

AstraZeneca submitted that if the Appeal Board did not rule a breach of Clause 25 it had nevertheless maintained high standards.

The circumstances discussed in detail below in relation to the Clause 2 ruling (namely, the impact that the alleged breach of undertaking would have, and how obvious the alleged breach was) were equally relevant to AstraZeneca's appeal of a breach of Clause 9.1.

AstraZeneca submitted that it maintained high standards and acted in a proportionate manner.

With regard to Clause 2, AstraZeneca submitted that the Panel had not provided any reasons for its conclusion that it had brought discredit upon and reduced confidence in the pharmaceutical industry. Whilst the supplementary information to Clause 2 included 'inadequate action leading to a breach of undertaking' as an activity 'likely' to be ruled in breach of Clause 2, an assessment must still be made on the facts of the particular case as to whether such ruling was warranted because, as the supplementary information also stated: 'A ruling of a breach of this clause is a sign of particular censure and is *reserved for such circumstances*' (emphasis added). However, the Panel's ruling appeared to have been made arbitrarily as it was based purely on the fact that failure to comply with an undertaking was cited in the Code as an activity likely to be in breach of Clause 2.

Even if the Appeal Board did not overturn the ruling of a breach of Clause 25, AstraZeneca submitted that a Clause 2 ruling was not warranted in this case; such a ruling would be entirely inappropriate and disproportionate. Whether or not the steps taken by a company to prevent a breach of an undertaking were adequate depended on all the circumstances, including the impact that any breach of undertaking would have, and how obvious the breach was. The circumstances relevant to the Appeal Board's assessment of the severity of the breach were set out below. As regards the impact that the alleged breach of undertaking would have, there were two main considerations: the historic nature of the material, and the non-promotional nature of the material. These were addressed separately below, followed by a consideration of how 'obvious' the alleged breach was.

With regard to the historic nature of the material AstraZeneca acknowledged that an undertaking related not only to the future dissemination of material, but also to material already disseminated and maintained by the company (which might include material on its website). However, in terms of material already disseminated before an undertaking was given, AstraZeneca submitted that there was a clear distinction to be drawn between material which remained in active circulation, and material which was of purely historic interest. This distinction lay in the severity of the breach; by its very nature, material of purely historic interest could not cause the same impact as material which was in active circulation. The presentation was of purely historic interest. In fact, it was of interest only to a vexatious complainant who had a particular agenda and who knew what he was looking for. This was supported by the fact that the presentation was:

- historic material from 2002
- not proactively distributed
- not tagged and therefore very difficult to find via an internet search engine without prior specific knowldege of the presentation contents
- held in a website archive
- difficult to find within the website itself (at least four clicks were needed to get to this content from the homepage).

AstraZeneca submitted that the presentation would no longer interest the investor community as investors would not look back to 2002 in order to make investment decisions. In these circumstances, AstraZeneca questioned in whose eyes the industry was discredited by the maintenance of the presentation on the company's corporate website.

AstraZeneca noted that whilst an undertaking was not limited to promotional material, the non-promotional nature of the presentation was of relevance to the assessment of whether it brought discredit upon and reduced confidence in the industry. This was because promotional material persuaded its audience to make a particular decision (namely, under Clause 1.2, to administer, consume, prescribe, purchase, recommend, sell, supply or use a particular medicine). Accordingly, promotional material necessarily had a different impact from non-promotional material. The potentially greater damage caused by promotional material was recognised in the wording of Clause 2 itself: 'Activities or materials *associated with promotion* must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry.' (emphasis added)

AstraZeneca submitted that whilst non-promotional material could be damaging (for example, if it misled), this was only a risk in so far as the material was actually relied upon. As explained above, the presentation would no longer be relied upon as a source of information due to its obviously historic nature (the presentations were ordered by date on the website).

AstraZeneca further submitted that whether or not a breach of undertaking was obvious or flagrant was relevant to the assessment of the adequacy of the action taken.

AstraZeneca submitted that in the present case, even if the Appeal Board disagreed with the company's interpretation of slide 18 (and upheld the ruling of a breach of Clause 25), the point was clearly open to interpretation. Accordingly, by not removing the presentation from its website, AstraZeneca could not be accused of inadequate action. In other words, the alleged breach was not so flagrant that a breach of Clause 2 was warranted.

AstraZeneca noted the ambiguity of the Code in relation to websites, in particular whether they fell within the scope of the Code or not. A review of Clauses 1.8, 24.1 and 24.2 indicated that material placed on a website outside the UK would only fall within the scope of the Code if:

- it was directed to a UK audience
- it was placed there by a UK company or an affiliate of a UK company or at the authority or instigation of a UK company and
- it specifically referred to the availability to the availability or use of the medicine in the UK.

AstraZeneca noted that in Case AUTH/2046/9/07, a global press release placed on a corporate website was held to fall outside the scope of the Code because it did not refer to the use or availability of the product within the UK.

AstraZeneca submitted that in the present case, the website (astrazeneca.com) was operated by AstraZeneca. It was therefore a UK website, and the Panel considered that material published thereon fell within the scope of the Code. This was notwithstanding that the presentation was not addressed to a specifically UK audience and did not specifically refer to the availability or use of the medicine in the UK. In these circumstances, it appeared illogical that materials that did not satisfy all three criteria above would, according to the Panel, fall within the scope of the Code if they were placed on the internet from within the UK, but not if they were placed on the internet outside the UK, as the impact would be the same. Specifically, it seemed perverse that the presentation fell within the scope of the Code, whilst similar business presentations by non-UK companies of interest to investors (including those based in the UK) would not fall within the scope of the Code if they did not meet all three criteria above.

In conclusion, AstraZeneca disagreed with the Panel's conclusion that the presentation breached the undertaking, and so it refuted the Panel's ruling of breach of Clause 25. However, in so far as the Appeal Board concluded that there was a breach of the undertaking, AstraZeneca strongly refuted the Panel's ruling of a breach of Clauses 9.1 and 2. Taking into account all the circumstances of the case, AstraZeneca submitted that it had acted appropriately, maintained high standards and had not brought discredit upon or reduced confidence in the industry. In particular, a ruling of breach of Clause 2 would give credence to a vexatious complaint at the cost of AstraZeneca's reputation; a common sense approach showed that the Panel's ruling was disproportionate.

**COMMENTS FROM THE COMPLAINANT**

The complainant alleged that, to date, AstraZeneca had admitted no wrongdoing whatsoever regarding Seroquel and its promotion in the US. The complainant provided links to two articles from 'The New York Times', one from 2010 entitled 'For $520 million, AstraZeneca Settles Case Over Marketing of a Drug', and another from 2011 entitled 'AstraZeneca Settles Most Seroquel Suits'; both articles discussed Seroquel.

The complainant alleged that from its launch, AstraZeneca knew that Seroquel caused significant weight gain. This was both time and dose related. When the complainant worked at AstraZeneca UK he was unwilling to sign off any advertising claims that said otherwise. He was told by his marketing colleagues this was 'a career limiting step'.

The complainant alleged that AstraZeneca knew that the claim 'weight-neutral' was never true. The complainant provided three links to US blog articles from 2011 discussing Seroquel, an AstraZeneca email from 1997 discussing Seroquel entitled 'weight gain', and a copy of a paper entitled 'From Evidence-based Medicine to Marketing-based Medicine: Evidence from Internal Industry Documents' (Spielmans and Parry 2010).

The complainant alleged that the issues he raised were both pertinent and current as demonstrated in a link he provided to an article in the Bermudan publication 'The

Royal Gazette online' from 2013 entitled 'Ace and XL sued by pharmaceutical giant' concerning an ongoing court case between AstraZeneca and two insurance companies regarding Seroquel.

The complainant submitted that he had repeatedly requested a meeting with AstraZeneca's chief medical officer to discuss his concerns, but his requests had been rebuffed.

The complainant stated that a vexatious litigant was defined as 'the bringer of an action that is brought without sufficient grounds for winning, purely to cause annoyance'. This could not be the case here as the Panel had found in his favour and AstraZeneca had appealed the decision. Consequently the complainant referred AstraZeneca to the reply given in Arkell vs Pressdram (1971).

**APPEAL BOARD RULING**

The Appeal Board noted that the presentation at issue appeared in the 'Investors' section of the AstraZeneca corporate website under 'Presentations and Webcasts' in a folder labelled 2002. The Appeal Board considered that, contrary to AstraZeneca's submission at the hearing, such information did not have the same status as a company's annual report or other announcements made to inform shareholders, the Stock Exchange and the like.

The Appeal Board decided that the presentation came within the scope of the Code as it was information about, *inter alia*, a prescription only medicine Seroquel, which appeared on AstraZeneca's website. In that regard the Appeal Board considered that it was irrelevant how old the data was. A potential investor in the company might look on AstraZeneca's website for information and find the presentation at issue.

The Appeal Board was concerned that AstraZeneca had not looked at archived material on its website in relation to the undertaking and assurance given in the previous cases. The Appeal Board noted AstraZeneca's submission that this was historical material. The Appeal Board further noted that the material was still in the public domain. There was no indication on the material itself that it was historical. The impression was that the material could still be current. The Appeal Board noted that an undertaking required that the promotional activity or use of the material in question and any similar material, if not already discontinued or no longer in use, would cease forthwith and that all possible steps would be taken to avoid a similar breach of the Code in the future. Details of certain actions taken by the company to implement the undertaking had to be provided, including the date on which the material was finally used or appeared and/or the last date on which the activity took place.

The Appeal Board noted AstraZeneca's submission that the presentation was clearly archived, no longer in use and not used proactively.

The Appeal Board noted that slide 18 was headed 'Seroquel – Strong differential advantage across the indications'. The Appeal Board noted that the first bullet point underneath the heading stated 'Broad-based efficacy' beneath which three sub-bullets stated 'as effective as other atypicals', 'efficacy in one week' and 'effective in the long-term'. The Appeal Board considered that together these three points contributed to the broad-based efficacy claim; each individual point on its own was not a claim for broad-based efficacy and would not be read as such. In the Appeal Board's view the lower half of the slide would be interpreted in the same way so that 'placebo-like EPS', 'placebo-like prolactin levels', 'low incidence of sexual dysfunction' and the claim at issue, 'weight-neutral in the long-term', would be seen to collectively contribute to Seroquel's 'Unique tolerability profile'. The Appeal Board did not consider that each point on its own would be read as a unique feature of Seroquel.

The Appeal Board noted that the undertaking given in Cases AUTH/2294/1/10, AUTH/2296/1/10 and AUTH/2297/1/10 related to the claim, 'The only atypical with placebo level EPS (including akathisia) and placebo level prolactin concentrations and a favourable weight profile across the full dose range'.

The Appeal Board considered that the presentation of the claim 'weight-neutral in the long-term' as one of four bullet points beneath the heading 'Unique tolerability profile' in the material at issue was such that it was not sufficiently similar to the claim at issue in Cases AUTH/2294/11/10, AUTH/2296/1/10 and AUTH/2297/1/10 for it to be covered by the undertaking given in those cases. Taking all the circumstances into account, the Appeal Board ruled no breach of Clause 25 and consequently no breaches of Clauses 2 and 9.1. The appeal was successful.

**Complaint received** **30 October 2012**

**Case completed** **13 February 2013**

# PHARMACOSMOS A/S V VIFOR PHARMA

## Contracts with Health Professionals

**Pharmacosmos A/S complained that exclusivity clauses in Vifor Pharma's consultancy contracts with health professionals were in breach of the Code.**

**Pharmacosmos alleged that several physicians had stated that they were unable to undertake consultancy work on behalf of Pharmacosmos as this would place them in breach of a pre-existing contract with Vifor.**

**Pharmacosmos was concerned that some of Vifor's consultancy arrangements with NHS service providers (organisations and individuals) were such that they constituted 'retainer' arrangements of the type banned by the Code and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and European Federation of Pharmaceutical Industries Associations (EFPIA) Codes. Whilst the confidential nature of some consultancy work was recognised there were clearly practical and legal issues that arose from exclusivity clauses including competition law, and barriers to market penetration. There were also patient safety issues and practical considerations for the NHS.**

**Pharmacosmos was conscious that it had not cited a specific example; however this complaint was based on the wording of the final inter-company response from Vifor:**

> **'We cannot comment on whether or not individuals can work on projects for both Vifor and Pharmacosmos at the same time as it will depend on the terms of their particular contracts in question'.**

**Pharmacosmos considered this was a clear admission that some contracts contained exclusivity clauses. Pharmacosmos sought confirmation that these were reserved for the most appropriate scenarios and did not, for example routinely prevent health professionals from speaking at meetings or attending advisory boards, etc, organised by other companies.**

**Pharmacosmos did not wish to interfere with the fair and reasonable contracting arrangements between Vifor and its suppliers and did not seek commercially sensitive information. However it was clear that exclusivity clauses were in use and depending on the wording of such clauses, a breach of the Code was therefore likely.**

**Pharmacosmos noted the requirements in the Code about the use of consultants and believed that these requirements should limit the use of exclusivity clauses to all but the most important confidential matters and should be used in highly specific and very limited circumstances.**

**Pharmacosmos submitted that it would be difficult to establish a need for an exclusivity clause as part of a speaker contract, for example, without implying an obligation on the part of the consultant.**

**Pharmacosmos stated that further considerations then arose as to why certain individuals were selected for the consultancy services – was it because the service was genuinely needed and the individual was the most appropriate, or was it to block that individual's availability to other companies.**

**Pharmacosmos stated there was recent case precedent whereby a complaint could be raised on the suspicion of inappropriate activity, even though the company complainant could not furnish detailed evidence (Cases AUTH/2479/2/12 and AUTH/2480/2/12). In those cases the complainants suspected inappropriate activity at a symposium but had not seen the slides or been present on the day. The case report indicated that the PMCPA sought copies of the slides and made a judgement based on the material reviewed.**

**Recognising the delicate nature of this complaint, Pharmacosmos stated that it had no desire to be sent copies of any template or specific contracts used by Vifor. Pharmacosmos hoped that the Authority would consider asking to see a random selection of recent and current contracts used by Vifor in addition to its general templates for routine consultancy arrangements.**

**The detailed response from Vifor Pharma is given below.**

**The Panel noted that its role was to consider the case in relation to the requirements of the Code rather than the IFPMA Code of Practice, the EFPIA Code on the Promotion of Prescription-Only Medicines to, and interactions with Healthcare Professionals or UK competition law.**

**The Panel noted Pharmacosmos' submission that its complaint was based on anecdotal feedback and its reference to Cases AUTH/2479/2/12 and AUTH/2480/2/12. The Panel considered that the nature of the evidence provided in those cases was very different to the present case. Turning to the present case, the Panel noted that the complainant had to establish its complaint on the balance of probabilities. The Panel would consider the evidence provided by both parties.**

**The Panel noted Pharmacosmos' allegation that some of the consultancy agreements between Vifor and health professionals and Vifor and NHS organisations were such that they constituted 'retainer' arrangements that were banned by, *inter***

***alia*, the Code. However, the Panel noted that the Code did not refer to retainer arrangements or exclusivity clauses and did not, *per se*, prevent such clauses in consultancy contracts. The Panel further noted that Pharmacosmos had submitted that there were some limited situations where exclusivity was appropriate. Vifor acknowledged that a small number of contracts between UK health professionals and its global organisation contained justifiable exclusivity clauses.**

**The Panel noted that consultancy agreements would necessarily cover legitimate commercial and business matters beyond the compliance requirements listed in the Code. Matters such as exclusivity terms would not be covered by the Code unless they otherwise rendered an agreement in breach of its requirements.**

**The Panel noted that Pharmacosmos had implied that some of the contracts between Vifor and health professionals existed to stop that individual working with any other company and that no genuine service to Vifor from the consultant was expected. The Panel noted that Pharmacosmos stated that several physicians were unable to undertake consultancy work for the company as that would place them in breach of a pre-existing contract with Vifor. Pharmacosmos had not identified those physicians or provided any evidence that their contract did not require the physicians to provide a genuine service to Vifor. The Panel noted that it had not seen any of Vifor's current consultancy agreements but noted that Vifors standard operating procedures (SOP), Contracts with Healthcare Professionals, clearly referred to all of the criteria for consultancy listed in the Code and the template contract contained a section headed 'Services' wherein the details of the consulting services could be added. The Panel noted that none of Vifor's standard operating procedure (SOP) template agreements contained exclusivity provisions. The Panel further noted Vifor's submission that no health professional retained by Vifor UK had such clauses in their agreements. A very small number of existing consultancy agreements between UK health professionals and global colleagues contained such provisions. The Panel noted that Pharmacosmos had accepted that exclusivity clauses were not unacceptable *per se*.**

**The Panel considered that Pharmacosmos had not, on the balance of probabilities, established that Vifor had used exclusivity clauses in the absence of expecting a genuine service for which there was a legitimate need, from the individual concerned. The Panel ruled no breach of the Code.**

Pharmacosmos A/S complained that exclusivity clauses in Vifor Pharma Limited's consultancy contracts with health professionals were in breach of the Code.

**COMPLAINT**

Pharmacosmos alleged that some of Vifor's consultancy arrangements did not or had not met the requirements of Clause 20 of the Code. Specifically, several practising physicians had stated that they were unable to undertake consultancy work on behalf of Pharmacosmos as this would place them in breach of a pre-existing contract with Vifor. This surprised Pharmacosmos and raised some genuine concerns. The company therefore sought clarification that Vifor did not routinely use exclusivity clauses in its consultancy contracts.

Pharmacosmos acknowledged that anything relating to contractual arrangements with third parties was delicate, as recognised in communications to Vifor and previously to the Authority. However Pharmacosmos was concerned that some of Vifor's consultancy arrangements with NHS service providers (organisations and individuals) were such that they constituted 'retainer' arrangements of the type banned by the IFPMA, EFPIA and ABPI Codes. Whilst the confidential nature of some consultancy work was recognised there were clearly practical and legal issues that arose from exclusivity clauses. This included matters of competition law and the barriers to market penetration, but there were also patient safety issues and practical considerations for the NHS.

In submitting this complaint and the accompanying inter-company exchanges, Pharmacosmos was conscious that it had not cited a specific example; this was directly related to those same contracts preventing the individuals (understandably) from sharing the details of the arrangements with Pharmacosmos. The basis for concern arose from feedback from potential health professional consultants to Pharmacosmos who had been approached; however this complaint was based on the wording of the final inter-company response from Vifor:

> 'We cannot comment on whether or not individuals can work on projects for both Vifor and Pharmacosmos at the same time as it will depend on the terms of their particular contracts in question'.

Pharmacosmos considered this was a clear admission that some contracts contained exclusivity clauses. Pharmacosmos sought confirmation that these were reserved for the most appropriate scenarios and did not, for example routinely prevent health professionals from speaking at meetings or attending advisory boards, etc, organised by other companies. Exclusivity in research contracts should also be highly tailored so as not to unnecessarily restrict the progress of medical science.

Pharmacosmos submitted that confidentiality clauses were of course of paramount importance. However exclusivity clauses were often unnecessary if the confidentiality clause was properly constructed. There were some situations where exclusivity was appropriate but Pharmacosmos considered that those situations were few. For example, it was established practice that a research unit and its employees could work on several trials concurrently; indeed, to do otherwise risked delaying important research that might ultimately benefit patient care. However a general exclusivity clause would prevent those individuals and units from working with other companies on a wide range of activities, from

conducting research to speaking at promotional and educational meetings. Exclusivity clauses would also have implications for the customers in terms of their necessary independence. For example it would prevent payors and health professionals from achieving a balanced level of interaction with industry and effectively tie them into one company. Such arrangements also gave rise to external perceptions regarding the appropriateness of such contracts as to the genuine need for the service to exist and the nature of the transparency declaration.

Pharmacosmos noted that the inter-company exchanges referred to competition law and the need for confidentiality in respect of detailed terms and conditions. This made the situation very difficult for Pharmacosmos to explore appropriately. Pharmacosmos did not wish to interfere with the fair and reasonable contracting arrangements between Vifor and its suppliers and did not seek commercially sensitive information regarding the nature of the arrangements and services or the specific contractual details, as made clear in inter-company dialogue. However it was quite clear from the final paragraph in Vifor's letter that exclusivity clauses were in use. Depending on the precise wording of those exclusivity clauses, a breach of Clause 20 of the Code was therefore likely.

Specifically, Clause 20 required that consultancy arrangements were:

- Genuine
- There was a clearly identified, legitimate need for the services
- The criteria for selecting the consultants must be related to the identified need
- The number of consultants must not be greater than the number needed to achieve the identified need
- Token consultancy arrangements must not be used
- The service provider must be required to declare their role as a consultant to the company

Taken together Pharmacosmos believed that these requirements should limit the use of exclusivity clauses to all but the most important confidential matters and should be used in highly specific and very limited circumstances.

Pharmacosmos submitted that it would be difficult to establish a need for an exclusivity clause as part of a speaker contract, for example, without implying an obligation on the part of the consultant. This effectively tied the consultant to that company and placed him/her in the implied position of needing to preserve relationships with that company in order to maintain future business, perhaps by looking more favourably on that company's products or seeing that company's representatives more often. It also called into question the nature of the declaration required from consultants when speaking in public or other occasions when they were required to make declarations concerning company consultancy arrangements; the reaction of the audience was likely to be different according to whether the consultant had accepted a fee for a particular event or whether that individual was exclusively tied to that company; the latter situation would surely require a different declaration even if such an arrangement was ever appropriate.

Pharmacosmos stated that further considerations then arose as to why certain individuals were selected for the consultancy services – was it because the service was genuinely needed and the individual was the most appropriate, or was it to block that individual's availability to other companies with its inevitable impact on the ability of competitor companies to provide educational services?

While Pharmacosmos did not wish to imply that Vifor had deliberately set out to block the availability of consultants to other companies, it was greatly concerned by the anecdotal feedback it had received.

Pharmacosmos stated there was recent case precedent whereby a complaint could be raised on the suspicion of inappropriate activity, even though the company complainant could not furnish detailed evidence (Cases AUTH/2479/2/12 and AUTH/2480/2/12). In those cases the complainants suspected inappropriate activity at a symposium but had not seen the slides or been present on the day. The case report indicated that the PMCPA sought copies of the slides and made a judgement based on the material reviewed.

Recognising the delicate nature of this complaint, Pharmacosmos stated that it had no desire to be sent copies of any template or specific contracts used by Vifor. Pharmacosmos hoped that the Authority would consider asking to see a random selection of recent and current contracts used by Vifor in addition to its general templates for routine consultancy arrangements; this might be for example, to see all contracts in a certain geography in a certain time period for a range of consultancy services.

Pharmacosmos very much hoped that the Authority would be able to explore its concerns in respect of unwarranted exclusivity clauses and could reassure Pharmacosmos that there was nothing to prevent the majority of health professionals from working on projects for both companies (unless, of course, there were particular and specific circumstances that would justify a unique arrangement in that regard). Pharmacosmos recognised the sensitivity in this matter for both companies.

**RESPONSE**

Vifor stated that Pharmacosmos' complaint was founded solely on it being advised by 'several' practising physicians that they were unable to undertake consultancy work on behalf of Pharmacosmos as this would place them in breach of a pre-existing contract with Vifor. Pharmacosmos had not provided any documentation or proof of its allegations, or even indicated the number of practising physicians, their location or the services under question.

Vifor considered that Pharmacosmos' allegation must also be viewed in light of the fact that, by Pharmacosmos' own admission, 'there were some situations where exclusivity was appropriate…'.

Vifor noted that Clause 20.1 of the Code set out a number of criteria which must be fulfilled when health professionals and appropriate administrative staff were used for genuine consultancy or other services. Clause 20.1 did not prohibit the use of non-compete provisions in consultancy agreements.

The general thrust of Pharmacosmos' complaint was that Vifor's policy was to engage certain health professionals not on the basis of a genuine consultancy requirement, but to block those individuals' availability to other companies. Vifor strongly refuted this allegation. All health professionals' engagements carried out by Vifor were genuine consultancies that complied with Clause 20.1.

- All consultancy work was carried out on the basis of written agreements, agreed in advance and detailing the nature of the services and the basis for payment.
- In each case, there was a clear legitimate need for the services.
- The criteria for selecting consultants were directly related to the identified need for the consultancy.
- The number of consultants retained was not greater than the number reasonably necessary to achieve the identified need.
- Appropriate records were maintained of the services provided.
- The hiring of each consultant was not an inducement to prescribe, supply, administer, recommend, buy or sell any medicine.
- All compensation for services was reasonable and reflected fair market value. Vifor did not enter into token consultancy arrangements.
- Consultancy contracts with health professionals required them to declare their consultancy for Vifor when writing or speaking on a topic related to the company.

Vifor stated that the fact that all health professional consultancies were genuine was further demonstrated by its standard operating procedures (SOPs) which referred to the arrangements for health professionals providing services to the company:

- SOP 007 (Contracts with Healthcare Professionals). Section 5, appendix A, specifically refered to Clause 20.1 and quoted directly from it
- SOP 212 (Approval of Meetings and Hospitality). Section 5.4 included direction on the criteria for use of speakers and section 5.7.1, appendix B, referred to advisory board participants

Both these SOPs covered all arrangements for health professionals providing any service for Vifor and gave clear guidance as to the criteria for engaging the health professionals as well as a clear procedure for the approval of arrangements (in both cases by two managers).

The SOPs also included template agreements (within the appendices) and none of these contained non-compete or exclusivity provisions.

Vifor stated that since the review of these SOPs earlier this year, Vifor also required global colleagues to adhere to the same SOPs. There were a number of existing consultancy agreements raised before this time, a very small number of which contained fully legitimate non-compete provisions. All such provisions were drafted in such as a way as to comply with applicable law and Clause 20.1.

Vifor considered that it was generally accepted in the industry that non-compete provisions represented a legitimate method to protect business interests, and were enforceable provided that they were proportionate and reasonable in their scope. The contracts it had with non-compete clauses numbered in the low single figures and had these clauses to protect the confidentiality and sensitivity of Vifor's legitimate research and/or commercial interests.

Finally, Vifor noted that the sentence in its letter, 'We cannot comment on whether or not particular individuals can work on projects for both Vifor and Pharmacosmos at the same time as this will depend on the terms of their particular contracts in question', was not a clear admission that some contracts contained exclusivity clauses as submitted by Pharmacosmos. It was simply a response to the very general questions posed by Pharmacosmos. As stated clearly above, no health professionals engaged by Vifor Pharma UK had non-compete clauses in their consultancy agreements, and while a very small number of existing consultancy agreements between UK health professionals and global colleagues contained non-compete provisions, they were in compliance with Clause 20.1 and applicable law.

Vifor submitted that it had always reserved the use of non-compete provisions for the most appropriate scenarios and, to answer Pharmacosmos' request for reassurance, it was not aware of anything that would prevent the majority of health professionals from working on projects for both companies. However, Vifor was not in a position to comment on the extent to which non-compete provisions imposed by Pharmacosmos might impact on the ability of a health professional to work for Vifor.

Vifor strongly refuted Pharmacosmos' allegation that some of its consultancy agreements with health professionals did not meet the requirements of the Code. Vifor denied a breach of Clause 20.

**PANEL RULING**

The Panel noted that its role was to consider the case in relation to the requirements of the Code rather than the IFPMA Code of Practice, the EFPIA Code on the Promotion of Prescription-Only Medicines to, and interactions with Healthcare Professionals or UK competition law.

The Panel noted that Pharmacosmos had alleged a breach of Clause 20 but had not cited the particular sub-clause. The allegations appeared to relate to Clause 20.1. Vifor had responded in relation to Clause 20.1 and thus the Panel considered the complaint in relation to Clause 20.1.

The Panel noted Pharmacosmos' submission that its complaint was based on anecdotal feedback and its reference to Cases AUTH/2479/2/12 and

AUTH/2480/2/12. The Panel considered that the nature of the evidence provided in Cases AUTH/2479/2/12 and AUTH/2480/2/12 was very different to the present case. Pharmacosmos had wrongly submitted that the complainant in Case AUTH/2480/2/12 had not seen the slides or been present at the presentation. A company employee had been at the meeting in question and had seen the material which was the subject of the complaint. Turning to the present case, the Panel noted that the complainant had to establish its complaint on the balance of probabilities. The Panel would consider the evidence provided by both parties.

The Panel noted Pharmacosmos' allegation that some of the consultancy agreements between Vifor and health professionals and Vifor and NHS organisations were such that they constituted 'retainer' arrangements that were banned by, *inter alia*, the Code. However, the Panel noted that Clause 20 did not refer to retainer arrangements or exclusivity clauses and did not, *per se*, prevent such clauses in consultancy contracts. The Panel further noted that Pharmacosmos had submitted that there were some limited situations where exclusivity was appropriate. Vifor acknowledged that a small number of contracts between UK health professionals and its global organisation contained justifiable exclusivity clauses.

The Panel noted that consultancy agreements would necessarily cover legitimate commercial and business matters beyond the compliance requirements listed in Clause 20.1. Matters such as exclusivity terms would not be covered by Clause 20.1 unless they otherwise rendered an agreement in breach of its requirements.

The Panel noted that Pharmacosmos had implied that some of the contracts between Vifor and health professionals existed to stop that individual working with any other company and that no genuine service to Vifor from the consultant was expected. The Panel noted that Pharmacosmos had submitted that several practicing physicians had stated that they were unable to undertake consultancy work for the company as that would place them in breach of a pre-existing contract with Vifor. Pharmacosmos had not identified those physicians or provided any evidence that their contract did not require them to provide a genuine service to Vifor. The Panel noted that it had not seen any of Vifor's current consultancy agreements but noted that SOP 007, Contracts with Healthcare Professionals, clearly referred to all of the criteria for consultancy listed in Clause 20.1 and the template contract contained a section headed 'Services' wherein the details of the consulting services could be added. The Panel noted that none of Vifor's SOP template agreements contained exclusivity provisions. The Panel further noted Vifor's submission that no health professional retained by Vifor UK had such clauses in their agreements. A very small number of existing consultancy agreements between UK health professionals and global colleagues contained such provisions. The Panel noted that Pharmacosmos had accepted that exclusivity clauses were not unacceptable *per se*.

The Panel considered that Pharmacosmos had not, on the balance of probabilities, established that Vifor had used exclusivity clauses in the absence of expecting a genuine service for which there was a legitimate need, from the individual concerned. The Panel ruled no breach of Clause 20.1.

**Complaint received** **8 November 2012**

**Case completed** **22 January 2013**

# GENERAL PRACTITIONER v NAPP

## Email promotion of Flutiform

**A general practitioner complained that Napp had sent an advertisement for Flutiform (fluticasone/formoterol) to his NHS email address. The complainant did not believe that a publicly funded email network for health professionals should be used for this purpose; doctors would be unduly influenced by this inappropriate advertising and their already overloaded in-trays would be unusable if they got swamped with unauthorised spam.**

**The detailed response from Napp is given below.**

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

**The Panel noted that when obtaining permission from health professionals to add them to their database, [and thus contact them through their NHS email account] the agency had made it clear to them that it would, from time to time, email information which might include, *inter alia*, pharmaceutical promotional material. It was clear that the company intended to email promotional material from pharmaceutical companies. The Panel noted Napp's submission that the complainant had been on the database for at least ten years and he had been contracted within the last year to confirm and update his details. During the reregistration process the complainant was made aware that he would receive promotional emails from time to time. The complainant had not responded to the Authority's request to comment on this information. On the material available, the Panel considered that there was evidence that the complainant had agreed to receive promotional material by email and it thus ruled no breaches of the Code.**

A general practitioner, complained about the promotion of Flutiform (fluticasone/formoterol) by Napp Pharmaceuticals Limited.

**COMPLAINT**

The complainant objected to a Flutiform advertisement from Napp which he had received on his NHS email, because he did not believe a publically funded email network for professionals should be infiltrated in this way and because it was in breach of the Code.

The complainant would like action taken over this as otherwise doctors would be unduly influenced by this inappropriate advertising and their already overloaded in-trays would become unusable if they got swamped with unauthorised spam.

When writing to Napp, the Authority asked it to respond in relation to Clauses 9.1 and 9.9 of the Code.

**RESPONSE**

Napp stated that the complainant had provided prior permission to receive promotional emails into his NHS email account from a third party agency (Clause 9.9). In addition, and in line with the supplementary information to Clause 9.9, the promotional email received by the complainant informed him how to unsubscribe. Napp believed that it had maintained high standards at all times (Clause 9.1).

Napp submitted that it contracted the agency to send the digital Flutiform advertisement at issue. The advertisement (ref UK/FLUT-12106) was certified in October 2012.

The agency provided a free resource for medical professionals employed in the NHS and private healthcare sectors in the UK. It was completely independent of the Department of Health and the NHS. Registered users had free access to information on the site, including information about prescription only medicines and medical devices, which could only be directed and accessed by health professionals who prescribed these products. The site included the latest information on the management of specific disease areas and medical conditions in an interactive format, including live online presentations and webcasts on the latest medical procedures. Users could only register via their NHS email account to prevent access by the public.

When completing their online registration form, a statement informed the health professional that completion of the form confirmed compliance with the terms and conditions which were accessible as part of the online registration process and were also included as part of email confirmation of continuing registration. These terms and conditions included the opt in policy (provided), which stated clearly that information provided might include pharmaceutical promotional materials and that users might opt out of receiving such materials without losing the remainder of the information service.

Further, approximately each year, every health professional user was contacted by the agency to confirm and update (if required) the information that they held. During this conversation, the health professional was reminded that they had consented to receive emails from the agency or its associated/affiliated companies, which included promotional information from pharmaceutical companies.

Napp submitted that the complainant had been registered with the free resource for at least ten years and the last time he was contacted was February 2012. The opt out rate was 0.25% so that it was not difficult to keep up-to-date with unsubscribers and there was no record of this being so.

The complainant re-registered electronically with the agency on 2 February 2012:

During the registration process the complainant was made aware that he would receive promotional emails from time to time.

The email advertisement for Flutiform informed the recipient how to unsubscribe to receiving further promotional emails, as required by the supplementary information to Clause 9.9.

In response to a request to provide further information setting out exactly what the complainant saw when completing the online registration, Napp submitted that the complainant had first registered with the free resource ten years ago. Details of the process for the complainant were provided. Step 1 was referred to as telephone contact. The caller would mention that the agency would from time to time send information by email about its associated/affiliated companies and their clients' products and services, which might include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information. This was also included in a follow up email (step 2). Step 3 was completion of the online registration which stated that 'completion of this online registration form confirms compliance with our terms and conditions'. Following submission of this form the complainant would receive confirmation that he was now a registered user of the free resource.

**PANEL RULING**

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

The Panel noted that when obtaining permission from health professionals to add them to their database, the agency had made it clear to them that it would, from time to time, email information about associated/affiliated companies, its clients and its clients' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information. It was clear that the company intended to email promotional material from pharmaceutical companies. The Panel noted the information provided by Napp regarding the inclusion of the complainant's details on the database. The complainant had not responded to the Authority's request to comment on this information. On the material available, the Panel considered that there was evidence that the complainant had agreed to receive promotional material by email and it thus ruled no breach of Clause 9.9. It consequently ruled no breach of Clause 9.1.

**Complaint received** **23 November 2012**

**Case completed** **20 March 2013**

# GENERAL PRACTITIONER v LILLY and BOEHRINGER INGELHEIM

## Email promotion of Trajenta

**A general practitioner complained that Lilly and Boehringer Ingelheim had sent an advertisement for Trajenta (linagliptin) to his NHS email address. The complainant did not believe that a publicly funded email network for health professionals should be used for this purpose; doctors would be unduly influenced by this inappropriate advertising and their already overloaded in-trays would be unusable if they got swamped with unauthorised spam.**

**The detailed response from Lilly and Boehringer Ingelheim is given below.**

**The Panel noted that the Code prohibited the use of email for promotional purposes except with the prior permission of the recipient. Whilst the material at issue had not been sent directly by Lilly and Boehringer Ingelheim it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.**

**The Panel noted that when obtaining permission from health professionals to add them to their database, [and thus contact them through their NHS email account] the agency had made it clear to them that it would, from time to time, email information which might include, *inter alia*, pharmaceutical promotional material. It was clear that the company intended to email promotional material from pharmaceutical companies. The Panel noted the companies' submission that the complainant had registered his details with the database in February 2012. During the registration process the complainant was made aware that he would receive promotional emails. The complainant had not responded to the Authority's request to comment on this information. On the material available, the Panel considered that there was evidence that the complainant had agreed to receive promotional material by email and it thus ruled no breaches of the Code.**

A general practitioner, complained about the promotion of Trajenta (linagliptin) by Eli Lilly and Company Limited and Boehringer Ingelheim Limited.

**COMPLAINT**

The complainant objected to a Trajenta advertisement from Lilly and Boehringer Ingelheim which he had received on his NHS email, because he did not believe a publically funded email network for professionals should be infiltrated in this way and because it was in breach of the Code.

The complainant would like action taken over this as otherwise doctors would be unduly influenced by this inappropriate advertising and their already overloaded in-trays would become unusable if they got swamped with unauthorised spam.

When writing to Lilly and Boehringer Ingelheim, the Authority asked them to respond in relation to Clauses 9.1 and 9.9 of the Code.

**RESPONSE**

Lilly (Case AUTH/2542/11/12) and Boehringer Ingelheim (Case AUTH/2543/11/12) submitted identical responses.

The companies stated that the email sent to the complainant's NHS email address highlighted the availability of a series of Trajenta webcasts initiated by the Boehringer Ingelheim and Eli Lilly and Co Diabetes Alliance (the Alliance) over the course of 2012. This series was put together in conjunction with and disseminated by a digital communications agency. Information about the webcasts was emailed to eligible health professionals who had previously registered their contact details into a database of NHS personnel. The agency had confirmed that it had a non-disclosure agreement with the database which allowed the transfer of confidential information.

The database of UK medical professionals at issue was independent of the Department of Health and the NHS. Health professionals could register their details with the database for information about prescription only medicines and medical devices. In addition the database provided all registered health professionals with information on the management of a variety of diseases and therapy areas. Health professionals could proactively access and register themselves on the database. Alternatively health professionals might be sent an email notification from an agency inviting them to register. All health professionals could only complete the registration once they had accepted the terms and conditions of the database website which might then allow information about affiliated organisations including promotional emails to be sent to them. Health professionals could opt in or out to receiving these communications.

Upon receipt of this complaint the companies discussed the issues with the digital communications agency which confirmed that the complainant registered his details with the database on 2 February 2012. Furthermore during the registration process the complainant was made aware that he would receive pharmaceutical company communications some of which might be promotional in nature. The exact wording was:

'In order to ensure that [the agency's] secure online database is the most up-to-date and comprehensive available, our data verification team will implement changes as-and-when they occur, based on revisions provided by you and your colleagues. [The agency] will from time to time send information by e-mail about our associated/affiliated companies and their clients' product and services, which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information. However, please be advised that we will not share your e-mails with any third parties. We welcome feedback on any aspect of the service. If you wish to suggest specific amendments or wish to draw our attention to certain matters, please feel free to contact us.'

Following this statement the complainant would have also been given the option of opting in/opting out to receiving such communications. The database overview clearly defined the registration process as well as the option to opt in or opt out.

Boehringer Ingelheim and Lilly were strongly of the opinion that they had wholly adhered to the requirements of the Code. The email communicating the availability of the Trajenta promotional webcasts was sent on their behalf by the agency. These emails were only sent to health professionals who had previously registered with the digital communications website and opted in to receiving communications from associated/affiliated companies. Hence the requirements of Clause 9.9 had been fully adhered to.

In conclusion, the companies strongly refuted the allegation of any wrongdoing. As evidenced by the documents provided in their response, the companies submitted that they had maintained high standards throughout this project.

In response to a request for further information, Boehringer Ingelheim and Lilly stated that the complainant was contacted by the agency's representative in January 2012 and following this initial telephone call, then received the preliminary email on 26 January 2012. The registration form was then completed and following this the complainant received his login details on 2 February 2012. Details were provided.

Lilly submitted that its response clearly demonstrated that the complainant had voluntarily provided his contact details including his professional email address to the agency. Before completing his registration, the complainant would have been made aware on separate occasions that he would be sent information regarding promotional activities undertaken by companies affiliated with the agency. This information would have been conveyed firstly by the agency's operative during the initial telephone call and then again in the preliminary email. The complainant would also have had the opportunity to opt out of receiving such communications by selecting this option in the preliminary email. The agency had confirmed that, to date, no opt out requests had been received from the complainant.

**PANEL RULING**

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

The Panel noted that when obtaining permission from health professionals to add them to their database, the agency had made it clear to them that it would, from time to time, email information about associated/affiliated companies, its clients and its clients' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information. It was clear that the company intended to email promotional material from pharmaceutical companies. The Panel noted the information provided by Lilly and Boehringer Ingelheim regarding the inclusion of the complainant's details on the database. The complainant had not responded to the Authority's request to comment on this information. On the material available the Panel considered that there was evidence that the complainant had agreed to receive promotional material by email and it thus ruled no breach of Clause 9.9. It consequently ruled no breach of Clause 9.1.

**Complaint received** **29 November 2012**

**Case completed** **20 March 2013**

# GENERAL PRACTITIONER v NAPP

## Email promotion of BuTrans

**A general practitioner complained that Napp had twice sent an advertisement for BuTrans (buprenorphine matrix patch) to her NHS email address. The complainant stated that she did not usually see representatives as she was concerned that her decisions about medicines might be compromised. As the complainant and her colleagues were looking at BuTrans/fentanyl patches in terms of their appropriate use it was unfortunate that she had received the email at issue. The complainant queried how her NHS email could be used in this way.**

**The detailed response from Napp is given below.**

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

**The Panel noted that when obtaining permission from health professionals to add them to their database [and thus contact them through their NHS email account] the agency concerned had made it clear that it would, from time to time, email information which might include, *inter alia*, pharmaceutical promotional material. It was clear that the agency intended to email promotional material from pharmaceutical companies. The Panel noted Napp's submission that the complainant had been invited to join the database in February 2012 and the terms and conditions would have been explained. The complainant had not responded to the Authority's request to comment on this information. On the material available, the Panel considered that there was evidence that the complainant had agreed to receive promotional material by email and it thus ruled no breaches of the Code.**

A general practitioner, complained about the promotion of BuTrans (buprenorphine matrix patch) by Napp Pharmaceuticals Limited.

**COMPLAINT**

The complainant stated that she was a busy GP who did not usually see representatives from pharmaceutical companies due to concerns of compromising her decision making of medication especially as prescribing lead for the practice. On two occasions, a BuTrans advertisement had been sent directly to her NHS email address.

As the complainant and her colleagues were specifically looking at BuTrans/fentanyl patches in terms of their appropriate use, the complainant considered that it was unfortunate that she received the advertisements in question. The complainant asked how her NHS email came to be available for use in this way.

When writing to Napp, the Authority asked it to respond in relation to Clauses 9.1 and 9.9 of the Code.

**RESPONSE**

Napp stated that the complainant had provided prior permission to receive promotional emails into her NHS email account from a third party agency (Clause 9.9). In addition, and in line with the supplementary information to Clause 9.9, the email promotion received by the complainant informed her how to unsubscribe. Napp believed that it had maintained high standards at all times (Clause 9.1).

Napp submitted that it contracted the agency to send the digital BuTrans advertisement at issue. The advertisement (ref UK/BUTR-12042) was certified in October 2012.

The agency provided a free resource for medical professionals employed within the NHS and the UK private healthcare sectors. It was completely independent of the Department of Health and the NHS. Registered users had free access to information on the site, including information about prescription only medicines and medical devices, which could only be directed and accessed by health professionals who prescribed these products. The site included the latest information on the management of specific disease areas and medical conditions in an interactive format, including live online presentations and webcasts on the latest medical procedures. Users could only register via their NHS email account to prevent access by the public.

When completing their online registration form, a statement informed the health professional that completion of the form confirmed compliance with the terms and conditions which were accessible as part of the online registration process and were also included as part of email confirmation of continuing registration. These terms and conditions included the opt in policy (provided), which stated clearly that information provided might include pharmaceutical promotional materials and that users might opt out of receiving such materials without losing the remainder of the information service.

Further, approximately once a year, every health professional user was contacted by the agency to confirm and update (if required) the information that it held. During this conversation, the health professional was reminded that they had consented

to receive emails from the agency or its associated/affiliated companies, which included promotional information from pharmaceutical companies.

Napp submitted that the complainant was invited by telephone to join the free resource on 3 February 2012. An email sent to her explained the registration process and terms.

The email advertisement for BuTrans at issue informed the recipient how to unsubscribe to receiving further promotional emails, as required by the supplementary information to Clause 9.9.

In response to a request to provide further information setting out exactly what the complainant saw when completing the online registration, Napp submitted that the complainant was invited to join the free resource in February 2012. Details of the process for the complainant were provided. Step 1 was telephone contact and the script included [agency] will from time to time send information by email about our associated/affiliated companies and their clients' product and services, which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information'. This was also included in a follow up email (step 2). Step 3 was completion of the online registration which stated that 'completion of this online registration form confirms compliance with our terms and conditions'. Following submission of this form the complainant received confirmation that she was now a registered user of the resource (3 February 2012).

**PANEL RULING**

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

The Panel noted that when obtaining permission from health professionals to add them to their database, the agency had made it clear to them that it would, from time to time, email information about associated/affiliated companies, its clients and its clients' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information. It was clear that the company intended to email promotional material from pharmaceutical companies. The Panel noted the information provided by Napp regarding the inclusion of the complainant's details to the database. The complainant had not responded to the Authority's request to comment on this information. On the material available, the Panel considered that there was evidence that the complainant had agreed to receive promotional material by email and it thus ruled no breach of Clause 9.9. It consequently ruled no breach of Clause 9.1.

**Complaint received** **6 August 2012**

**Case completed** **15 October 2012**

CASES AUTH/2546/11/12, AUTH/2547/11/12, AUTH/2548/11/12, AUTH/2552/11/12, AUTH/2554/11/12, AUTH/2556/11/12, AUTH/2559/11/12, AUTH/2560/11/12, AUTH/2561/11/12 AND AUTH/2563/11/12

# ANONYMOUS HEALTH PROFESSIONALS v ASTELLAS, ALLERGAN, BAXTER, FERRING, IPSEN, JANSSEN, ORION, PFIZER, RECORDATI AND TAKEDA

## Sponsorship of a meeting

**An anonymous non-contactable group describing themselves as NHS health professionals complained that a number of companies had breached the Code when supporting the annual meeting organised by the Irish Society of Urology (ISU), and held in Belfast in September 2012.**

**The complainants noted that the meeting was held in the UK and UK health professionals attended. Most of the employees from the companies were based in the UK. The first page of the scientific programme featured photographs of the very luxurious, 5 star venue and nearby attractions; this placed undue emphasis on non-scientific aspects of the meeting. The welcome message on the first page of programme read 'The social aspect of this meeting is extremely important and the two evening events promise great enjoyment. The unique opportunity to have our gala dinner in Stormont was one that we couldn't pass over!' Most of a second day of the meeting was dedicated to playing golf and leisure activities as clearly marked in the programme.**

**The complainants alleged that the pharmaceutical companies that supported this meeting seriously breached the Code on the grounds of excessive hospitality.**

**The detailed responses from Astellas, Allergan, Baxter, Ferring, Ipsen, Janssen, Orion, Pfizer, Recordati and Takeda are given below.**

**The Panel noted that the meeting had been held in Northern Ireland and thus the ABPI Code applied. The Panel also noted that it was an established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.**

**The 'programme at a glance' stated that the meeting started on the Friday with registration followed by scientific/educational sessions from 9am. The conference dinner was held at 7pm. On the Saturday scientific/educational sessions ran from 9am after the annual general meeting until 12.10pm when the meeting closed with lunch. The programme stated '12.50 Departure for Golf, [named golf club]' and '18.45 Departure for Gala Dinner, Parliament Buildings, Kindly sponsored by [a Northern Ireland named politician]. The more detailed programme stated that the conference dinner on 21 September included a 'Drinks reception kindly sponsored by Astellas Pharma Co Ltd'. The notes page of the programme (penultimate page) stated 'An educational grant was provided by Allergan Ltd to the Irish Society of Urology to support this independent course. Allegan [sic] has had no involvement in the logistics, design or content of the course'. On the back page of the programme was a list of companies (including the ten at issue in these cases) which the ISU thanked for their support.**

**The Panel noted that the Immediate Past President of the ISU (who was President when the meeting took place and who appeared to have received a copy of the complaint) had written to the companies to address some of the inaccuracies in the complaint and clarify the role of the pharmaceutical companies. The past president stated that he chose the meeting venue and the venue for the gala dinner. Golf was arranged as a courtesy for delegates by the ISU. Anyone who played golf paid for it themselves and no pharmaceutical company was involved in this in any way. The golf was arranged for after the scientific meeting had finished and when the trade exhibitors and indeed some attendees had already left. The letter stated that no pharmaceutical company had any hand, act or part in any of the issues raised in the complaint, which, in the past president's view, was, by definition, spurious as it was unsigned and mischievous. The meeting was solely organised by the ISU and pharmaceutical companies were invited to exhibit. Delegates were responsible for their own expenses during the meeting, including registration fees, meals and accommodation. The letter finished by stating that the ISU would continue to organise its own meeting and at a venue of its choosing.**

**The Panel noted that pharmaceutical companies could be involved in meetings organised by third parties including by way of general sponsorship, sponsoring a specific part of the meeting, sponsoring delegates to attend or paying to exhibit. Further details are given in the Panel's general comments below. Each case would be considered on its own merits bearing in mind all the relevant circumstances. The overall impression of the arrangements was an important consideration.**

**The Panel noted that the ISU could organise whatever meetings it wanted to for its own members but the involvement of pharmaceutical companies with various activities meant the meeting at issue was covered by the Code. Most of**

**the pharmaceutical companies had only exhibited at the meeting. Two of the companies had provided sponsorship.**

**The Panel considered that the scientific content was not unreasonable. It consisted of one and a half days of education. The programme stated '9 CPD [continuing professional development] credits'. The Panel noted that a number of companies paid for exhibition space and considered that the amount charged did not appear unreasonable. The Panel noted that the exhibitor's fee included 3 tickets for the conference dinner. (The Panel noted that the ISU had informed some of the companies that the cost of the exhibition stand at €1,850 represented around 2% of the total cost of hosting the scientific programme. Nineteen companies had supported the meeting thus covering 38% of the costs. The ISU stated that the sponsorship from exhibitors did not assist with the expense of the social functions including golf, conference dinner, gala dinner or accommodation). The exhibitor registration form included a section headed 'social programme' which stated that tickets for the conference dinner and gala dinner were €60 and €70 respectively. There was no mention of golf on this form. The Panel did not know how much the ISU charged for the golf. The Panel noted that the meeting programme referred to the golf and the gala dinner. The Panel considered that in this regard the two events were part of the formal proceedings of the meeting albeit that they occurred after the medical/scientific sessions had finished and had to be paid for by the delegates themselves.**

**The Panel further noted that the declaration of pharmaceutical company sponsorship on the back page of the programme was not clear as to exactly what had been supported. It was not unreasonable to assume that the companies listed had supported everything in the programme including the golf and gala dinner.**

**The Panel was also mindful of the established principle that a pharmaceutical company could not support a third party activity if that activity was itself in breach of the Code.**

**The Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted the companies' submissions regarding the hotel's conference facilities but considered that other non-luxurious venues would have had adequate conference facilities.**

**Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Astellas, Baxter, Ferring, Ipsen, Janssen, Orion, Pfizer, Recordati and Takeda in breach of the Code.**

**The Panel noted that in addition to paying to exhibit, Astellas Ireland had paid for what was described in the programme as a drinks reception. The itemised bill was paid at 1.15am. The receipt recorded 125 covers and 265 items. Astellas UK stated that the drinks reception was immediately before dinner. The Panel noted that attendees were given two tickets which allowed them to obtain two drinks of their choice; Astellas had no control over what was provided. In the Panel's view this was unacceptable. The itemised bill showed that a number of spirits had been ordered as well as 2 Irish coffees, 3 liqueurs and other drinks which were more likely to be consumed after dinner than before. There was no way of knowing at what time the drinks were provided.**

**Astellas Ireland had also supported the attendance of 6 delegates from the Irish Republic. Some of these delegates had their accommodation paid for, one dinner had been paid for and some registration fees.**

**The Panel considered that by paying the accommodation, subsistence and registration costs of some delegates and its lack of control at the drinks reception rendered the level of hospitality provided by Astellas inappropriate; high standards had not been maintained. Breaches of the Code were ruled.**

**Allergan had not exhibited at the meeting and its support was for the venue hire and AV costs. The company had clearly stated its terms of support in a letter to the Royal College of Surgeons in Ireland (RCSI).**

**The penultimate page of the programme referred to the educational grant provided by Allergan. It was for the same amount as that paid for an exhibition stand. There was no indication that the majority of companies listed on the back page had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met by Allergan and the Panel ruled a breach.**

**The Panel noted that Baxter, Ferring, Ipsen, Janssen, Orion, Pfizer, Recordati and Takeda had not sponsored any health professional to attend the meeting by paying for accommodation, subsistence or registration fees. Allergan, Baxter, Ferring, Ipsen, Janssen, Orion, Pfizer, Recordati and Takeda had supported the venue hire and AV costs of the meeting. The Panel considered that the venue was on the limits of acceptability given its 5 star rating but nonetheless ruled no breach of the Code.**

**The Panel noted that Ferring did more than pay to exhibit; one employee had attended the gala dinner.**

**The Panel considered that purchasing a ticket for the gala dinner was inappropriate. Although health professionals paid for their own tickets it was not acceptable for a company to be involved in such an event. The educational content of that day (3 hours 40 minutes in the morning) did not justify the gala dinner in the evening which appeared to be a social event; high standards had not been met in this regard. Breaches of the Code were ruled.**

**The Panel noted that in addition to paying to exhibit, Janssen had purchased a ticket for the gala dinner. Although the dinner ticket had not been used the Panel considered that its purchase showed an intent to attend. It noted its previous rulings that the education content did not justify the gala dinner which appeared to be a social event and that high standards had not been met in this regard. Breaches of the Code were ruled.**

**The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its rulings above and decided that, on balance, the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled in relation to all the companies referred to in this case report.**

An anonymous non-contactable group describing themselves as NHS health professionals complained that a number of companies had breached the Code when supporting the annual meeting organised by the Irish Society of Urology (ISU) and held at the Culloden Estate and Spa, Holywood, Belfast in September 2012.

**COMPLAINT**

The complainants noted that:

- The meeting was held within the UK and significant numbers of attendees were UK health professionals. Most of the employees from the companies named by the complainants were based in the UK.

- The meeting was held at a very luxurious, 5 star venue, described on its website as:

***'Built for a Bishop, Fit for a King***
***This is 5 star. This is red carpet romance. Platinum standard pleasure. This is something very special indeed.*** [emphasis added]

*Nestled high in the Holywood hills and overlooking Belfast Lough,* ***is the Hastings Group's most luxurious hotel,*** *The Culloden Estate & Spa. Originally built as an official palace for the Bishops of Down, this stunning spot, set in 12 acres of secluded gardens,* ***is the jewel in the crown of County Down.*** [emphasis added]

***Come for business. Indulge in an ESPA Spa treatment. Head for Royal Belfast Golf Club.'*** [emphasis added]

- The first page of the scientific programme featured photographs of the venue and nearby attractions; this placed undue emphasis on non-scientific aspects of the meeting.

- The welcome message from the President of the ISU on the first page of programme read 'The social aspect of this meeting is extremely important and the two evening events promise great enjoyment. The unique opportunity to have our gala dinner in Stormont was one that we couldn't pass over!'

- A significant part of a second day of the meeting (the majority of it indeed!) was dedicated to playing golf and leisure activities and that was very clearly marked in the programme:

  **'12.50 Departure for Golf; Blackwood Golf Club'** [emphasis added]

The complainants alleged that all of the pharmaceutical companies that supported this meeting seriously breached the Code on the grounds of excessive hospitality.

The complainants submitted that this was of the upmost importance in times where NHS budgets were cut across the board and where the public increasingly scrutinised their profession.

When writing to the companies named, the Authority asked each to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

**CASE AUTH/2546/11/12 ASTELLAS**

**RESPONSE**

Astellas Pharma Ltd (UK Affiliate) stated that it had good processes for meetings review and approval. Astellas took particular care to ensure that the Code was upheld in both letter and spirit and so it was dismayed to realise that an Astellas organisation supported a meeting in the UK without its knowledge. In this case it was the Irish affiliate, Astellas Pharma Co Ltd, however Astellas Pharma Ltd accepted that it was responsible for ensuring compliance with the Code for meetings which involved UK health professionals and/or took place in the UK.

Astellas submitted that the ISU was a respected academic society which covered the whole of Ireland. Its annual scientific meeting was sometimes held in Northern Ireland although most of the delegates were from the Republic of Ireland. It was regrettable that the Irish affiliate forgot that this would have to be approved by the UK although in mitigation there was a growing tendency in academia to treat the whole of Ireland as a single country. However, the Irish affiliate had recognised the need to further raise the awareness of its procedures in this regard and a compliance manager for Astellas Europe had already emailed a reminder to all affiliates as a result of this complaint.

The meeting was approved by the Irish affiliate in line with the Irish Pharmaceutical Healthcare Association (IPHA) Code of Practice. Astellas Ireland received the exhibitor booking from ISU on 18 May 2012 and approved the meeting on 11 September 2012. Astellas UK understood that a final programme was available on 11 September for inspection.

Astellas did not advertise the event and therefore no materials were produced. Astellas's sponsorship of the event was acknowledged on the last page of the programme.

All sponsoring companies were charged a flat exhibitor's fee of €1,850 which entitled them to three places at the conference dinner on the Friday evening. Astellas Ireland paid for an additional dinner place (€60). A letter from the President of the ISU at the time, confirmed that the venue, post-meeting golf and post-meeting gala dinner were entirely organised by the ISU and that the monies raised were not used to pay for any of these events.

Astellas UK noted that six delegates from the Irish Republic had some of their costs paid by Astellas Ireland. Five delegates had their registration paid for and five had accommodation paid for. This was considered by the Irish affiliate to be consistent with the IPHA Code. No UK delegates were sponsored to attend by either Astellas Ireland or Astellas UK.

The ISU meeting was a main event for urologists in the whole of Ireland. The programme was academic and the meeting itself was the main attraction and not the venue, golf or gala dinner. No pharmaceutical company was involved in choosing the venue. While accepting that this was a 5 star venue and therefore would not normally be approved, it was a well known and highly convenient conference venue in Northern Ireland; it was close to road and air links and so it made logistical sense for such a meeting to be held there. In addition Astellas noted that the hotel had no golf course. Bearing in mind that no UK delegate was sponsored by Astellas to attend and that Astellas had no input into the choice of this venue, Astellas did not believe that there had been a breach of Clause 19.1.

The Astellas stand had no promotional materials available to hand out and there were only clinical papers approved for use which could be distributed on request.

The Friday evening conference dinner took place at the meeting venue and was attended by four Astellas Ireland personnel. A drinks reception, which the ISU invited Astellas to sponsor, was held immediately before the dinner in the hotel. Itemised bar receipts were provided. Delegates were given two tickets which allowed them to have two soft or alcoholic drinks; they had to pay for any further drinks themselves. Astellas did not know how many delegates attended but assumed that the vast majority of the 132 registered delegates were present, bearing in mind the delegate geographical breakdown (95 from the Republic of Ireland, 23 from Northern Ireland and 14 from mainland Britain). The bill for drinks was £1012.40 which was, on average, around £7.60 to £9 per person which Astellas did not consider excessive or beyond anything the delegates would reasonably have paid for themselves. Astellas did not provide any funding for drinks at the main conference dinner. The supplementary information to Clause 19.1 of the Code stated that 'The provision of hospitality is limited to refreshments/subsistence (meals and drinks), accommodation, etc…' and therefore Astellas did not consider that this in itself was a breach of the Code.

With regard to the golf organised after the official close of the meeting, Astellas UK submitted that it had been reassured by its Irish colleagues that no Astellas employee played golf and that Astellas did not subsidise the golf in any way. The programme made it very clear that golf took place after the meeting had officially closed and was therefore, in Astellas' view, not part of the meeting which again made this not necessarily unacceptable, although Astellas questioned the wisdom of advertising it on the programme itself rather than in a separate communication unrelated to the scientific programme.

Similarly, Astellas had no input into the choice of the venue for the gala dinner (Stormont Buildings) and no Astellas employee attended this dinner. No subsistence was given by Astellas towards the costs of this dinner and therefore Astellas UK did not believe, despite its lack of knowledge of this event, that it would have found this to be unacceptable had it had the chance to review this before the event, given that this dinner also occurred after the official close of the meeting. The ISU clearly retained the right to organise its own meetings and the lack of attendance by Astellas employees and of any subsidy of social activities by Astellas in its opinion meant that this was not in breach of Clause 19.1.

In summary, although Astellas UK was unaware of this meeting taking place and had not approved it under its procedures it was confident that the meeting could have been approved in principle as no pharmaceutical company had any input into the meeting content or venue or to any social activity, except for the sponsorship of the Friday evening pre-dinner drinks by Astellas. The supplementary information to Clause 19.1 stated that it was unacceptable for companies to sponsor meetings which were 'wholly or mainly of a social or sporting nature'. The programme clearly demonstrated that the meeting was mainly scientific in nature with one 'social event' – the conference dinner occurring during the meeting and two other social activities – golf and the gala dinner – taking place clearly after the meeting had officially finished and the pharmaceutical companies had dismantled their stands and left. Astellas submitted that as delegates had to eat somewhere, a dinner occurring during the scientific part of the meeting was not unreasonable and would provide further networking opportunities for delegates. In Astellas UK's view it was regrettable that undue emphasis was placed on the social events in the programme. This would have concerned Astellas UK and it would have wished to see the balance of the welcome message focus on the

scientific content. Astellas UK submitted, however, that the hospitality provided by Astellas was not excessive and it therefore denied a breach of Clause 19.1.

Astellas UK stated that it was regrettable that its Irish affiliate forgot to get UK approval for this meeting but bearing in mind the unusual situation in Ireland it was perhaps an understandable mistake and Astellas did not consider it merited a ruling that high standards had not been maintained by the UK affiliate (Clause 9.1). The Irish affiliate had improved the awareness of its procedures in this regard and a reminder from Astellas Europe was sent to all affiliates. Similarly Astellas submitted that, given the findings of its investigation, it had not brought discredit upon or reduced confidence in the industry's reputation (Clause 2

**GENERAL COMMENTS FROM THE PANEL (apply in all cases)**

The Panel considered the complaint in relation to the ABPI Code only. The meeting had been held in Northern Ireland and thus the ABPI Code applied. The supplementary information to Clause 1.8 made it clear that an activity carried out in the UK must comply with the UK Code regardless of whether or not UK health professionals attended. The Panel also noted that it was an established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Before considering each individual case, the Panel reviewed relevant requirements of the Code in relation to meetings, hospitality and sponsorship.

Clause 19.1 stated that meetings must be held in appropriate venues conducive to the main purpose of the event. Hospitality must be strictly limited to the main purpose of the event and must be secondary to the purpose of the meeting ie subsistence only. The level of subsistence offered must be appropriate and not out of proportion to the occasion. The costs involved must not exceed that level which the recipients would normally adopt when paying for themselves. The supplementary information to Clause 19.1 made it clear that the provision of hospitality was limited to refreshments/subsistence, accommodation, genuine registration fees and the payment of reasonable travel costs which a company might provide to sponsor a delegate to attend a meeting. The venue must not be lavish, extravagant or deluxe and companies must not sponsor or organise entertainment such as sporting or leisure events. In determining whether a meeting was acceptable or not consideration needed to be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, subsistence provided and the like. It should be the programme that attracted delegates and not the associated hospitality or venue. The supplementary information also stated that a useful criterion in determining whether the arrangements for any meeting were acceptable was to apply the question 'would you and your company be willing to have these arrangements generally known?' The impression that was created by the arrangements for any meeting must always be kept in mind.

The Panel noted that the welcome message from the ISU President, printed in the meeting programme, referred to the fact that the ISU was an all island society and that the annual meeting was more usually held in the Republic of Ireland. It also referred to a record number of abstracts being submitted for consideration but the ISU was unable to accommodate a significant number in the programme. The ISU hoped that this trend of increased numbers of submissions would continue in the future and in so doing raise the scientific profile and standard of the meeting which was already high. The welcome referred to three speakers before a short paragraph which described the social aspect of the meeting as 'extremely important and the two evening events promise great enjoyment. The unique opportunity to have our gala dinner in Stormont was one that we couldn't pass over!'. The President also referred to the participation of 'our colleagues from the pharmaceutical and medical equipment industries' without which 'a meeting such as this would not be possible and we are very grateful for their involvement'. The President thanked all who would be presenting at the meeting or chairing parts of it, hoped the meeting proved to be educational and enjoyable and that delegates enjoyed 'this beautiful area of County Down'. The President's message concluded by inviting attendance at the 2013 meeting which would be held at a named venue in Wicklow.

The 'programme at a glance' stated that the meeting started on Friday 21 September 2012 with registration followed by scientific/educational sessions from 9am. The conference dinner was held at 7pm. On Saturday 22 September scientific/educational sessions ran from 9am after the annual general meeting until 12.10pm when the meeting closed with lunch. The programme stated '12.50 Departure for Golf, [named golf club]' and '18.45 Departure for Gala Dinner, Parliament Buildings, Kindly sponsored by [a Northern Ireland named politician]. The more detailed programme stated that the conference dinner on 21 September included a 'Drinks reception kindly sponsored by Astellas Pharma Co Ltd'. The notes page of the programme (penultimate page) stated 'An educational grant was provided by Allergan Ltd to the Irish Society of Urology to support this independent course. Allegan (sic) has had no involvement in the logistics, design or content of the course' on the back page of the programme was a list of companies (including the ten at issue in these cases) which the ISU thanked for their support.

The Panel noted that the Immediate Past President of the ISU (who was President when the meeting took place and who appeared to have received a copy of the complaint) had written a letter to the companies in which he stated that he would address some of the inaccuracies in the complaint and clarify the role of the pharmaceutical companies in the conduct of the meeting. The past president stated that the venue was chosen solely by him. No pharmaceutical company had any part in the choice of venue. Stormont Castle was also chosen by him as the location for the gala

dinner. No pharmaceutical company had any input into this event. The golf was arranged as a courtesy for delegates by the ISU. Anyone who played golf on that day paid for it themselves and again no pharmaceutical company was involved in this in any way. The golf was arranged for a time after the scientific meeting had finished and when the trade exhibitors and indeed some attendees had already left. The letter stated that no pharmaceutical company had any hand, act or part in any of the issues raised in the complaint, which, in the past president's view, was, by definition, spurious as it was unsigned and mischievous. The meeting was solely organised by the ISU and pharmaceutical companies were invited to exhibit at the trade exhibition during the course of the meeting in a room provided for this purpose. All delegates were responsible for all of their own expenses during the meeting, including registration fees, meals and accommodation. The letter finished by stating that the ISU would continue to organise its own meeting and at a venue of its choosing.

The Panel noted that there were a number of ways that pharmaceutical companies could be involved in meetings organised by third parties. This included general sponsorship of such a meeting, sponsoring a specific part of it, sponsoring delegates to attend or paying to exhibit.

With regard to the implications of a pharmaceutical company paying to exhibit at a third party meeting, the Panel considered that if a company only paid for an exhibition stand then this would not necessarily be in breach of the Code even if aspects of the meeting did not meet the requirements of the Code. In the Panel's view certain conditions were relevant. Firstly, the exhibition must be a formal part of a genuine scientific or medical meeting independently organised, for example by a learned society. The meeting overall must not be of a wholly or mainly social or sporting nature. Secondly, the amount paid for the exhibition space must cover the genuine costs of putting on the exhibition and not be used to pay for or subsidise activities that did not meet the requirement of the Code. Thirdly, preferably a number of other companies must also be exhibiting. Fourthly, it should be made clear to all attendees that the pharmaceutical company had only paid for a trade stand. Fifthly, the venue must be appropriate and broadly in line with the requirements of the Code. Finally, apart from paying for an exhibition stand the company must have no other involvement in the meeting or in the arrangements for it. This would include sponsoring delegates to attend or sponsoring other aspects of the meeting. Each case would be considered on its own merits bearing in mind all the relevant circumstances. The overall impression of the arrangements was an important consideration.

With regard to the meeting in question, the Panel noted that it was organised by the ISU. The ISU was of course free to organise whatever meetings it wanted to for its own members. If there had been no involvement from pharmaceutical companies then the meeting would not have been covered by the Code. The involvement of the pharmaceutical companies with various activities meant the matter was covered by the Code. Most of the pharmaceutical companies had only exhibited at the meeting. Two of the companies had provided sponsorship.

The Panel considered that the scientific content was not unreasonable. It consisted of one and a half days of education. The programme stated '9 CPD [continuing professional development] credits'. The Panel noted that a number of companies paid for exhibition space and considered that the amount charged did not appear unreasonable. The Panel noted that the exhibitor's fee included 3 tickets for the conference dinner. (The Panel noted that the ISU had informed some of the companies that the cost of the exhibition stand at €1,850 represented around 2% of the total cost of hosting the scientific programme. Nineteen companies had supported the meeting thus covering 38% of the costs. The ISU stated that the sponsorship from exhibitors did not assist with the expense of the social functions including golf, conference dinner, gala dinner or accommodation). The exhibitor registration form included a section headed 'social programme' which stated that tickets for the conference dinner and gala dinner were €60 and €70 respectively. There was no mention of golf on this form. The Panel did not know how much the ISU charged for the golf. The Panel noted that the meeting programme referred to the golf and the gala dinner. The Panel considered that in this regard the two events were part of the formal proceedings of the meeting albeit that they occurred after the medical/scientific sessions had finished and had to be paid for by the delegates themselves.

The Panel further noted that the declaration of pharmaceutical company sponsorship on the back page of the programme was not clear as to exactly what had been supported. It was not unreasonable to assume that the companies listed had supported everything in the programme including the golf and gala dinner.

The Panel was also mindful of the established principle that a pharmaceutical company could not support a third party activity if that activity was itself in breach of the Code.

**PANEL RULING IN CASE AUTH/2546/11/12**

The Panel noted Astellas UK's submission that its Irish affiliate forgot to get UK approval for this meeting. The Panel considered that the Irish affiliate should know that any meeting which it sponsored in Northern Ireland was covered by the UK Code. This was clearly set out in the supplementary information to Clause 1.8 of the ABPI Code and reflected requirements in the EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals. The Panel noted that Astellas Europe had taken action to prevent such an oversight happening again.

The Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Astellas UK's submission regarding the conference facilities offered by the venue but considered that other non-luxurious venues would have had adequate

conference facilities. The Panel further noted that Astellas's External Meeting Policy clearly stated that 5 star hotels should not be used for meetings.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Astellas UK in breach of Clause 9.1.

The Panel noted that Astellas's involvement went further than paying for a trade exhibition. Astellas Ireland had paid £1012.40 for what was described in the programme as a drinks reception. The itemised bill was paid at 1.15am. The receipt recorded 125 covers and 265 items. Astellas UK stated that the drinks reception was immediately before dinner. The Panel was concerned about the arrangements in that attendees were given two tickets which allowed them to obtain two drinks of their choice; Astellas had no control over what was provided. In the Panel's view this was unacceptable. The itemised bill showed that a number of spirits (gin, whiskey, vodka and rum) had been ordered and it also included 2 Irish coffees, 3 liqueurs and a number of other drinks which were more likely to be consumed after dinner than before dinner. There was no way of knowing at what time the drinks were provided.

The Panel also noted that Astellas Ireland had supported the attendance of 6 delegates from the Irish Republic. Some of these delegates had their accommodation paid for, one dinner had been paid for and some registration fees.

The Panel considered that by supporting health professionals' attendance by paying for accommodation, subsistence and registration fees and its lack of control regarding drinks on the evening of the conference dinner rendered the level of hospitality provided by Astellas inappropriate. A breach of Clause 19.1 was ruled. High standards had not been met in this regard and a further breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its rulings above and the submission that Astellas had not paid for delegates to attend the golf or gala dinner. It decided that, on balance, the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

**CASE AUTH/2547/11/12 ALLERGAN**

**RESPONSE**

Allergan stated that it received a request in December 2011 for sponsorship from the Royal College of Surgeons in Ireland (RCSI) to support the ISU Annual Meeting. The meeting was of an extremely high educational standard with a full programme of scientific sessions, guest lectures and a moderated poster session with top experts in the field of urology. A copy of the programme for the previous annual meeting was provided by the RCSI for reference.

Allergan was informed of the meeting venue in Northern Ireland and that there would be attendees from both the Republic of Ireland and Northern Ireland.

The request for support for the meeting was reviewed and approved as a sponsorship request. Allergan had provided €1,850. A letter sent to the RCSI detailed the terms of Allergan's support, the €1,850 was to support the venue hire and AV costs for the meeting. Allergan requested that the following statement be added to all the associated materials produced in relation to the event:

'An educational grant was provided by Allergan Ltd to the Irish Society of Urology to support this independent course. Allergan has had no involvement in the logistics, design or content of the course.'

When considering the sponsorship request Allergan was aware of the proposed location and that the format would be similar to the 2011 Annual Meeting. It did not have the proposed 2012 agenda.

Allergan considered that the venue was acceptable. It was chosen by the ISU and met the logistical requirements of the delegates. The hotel was convenient for delegates flying in from around Ireland and the costs were not dissimilar to other business/congress hotels in Ireland. The complainants' description of the hotel reflected the hotel's marketing on its website, which was designed to attract customers to the venue.

Allergan understood that lunch and an evening meal would be provided on day 1 (Friday). There was a lunch break of 55 minutes and an evening conference BBQ in 2011 (lunch and a Conference Dinner in 2012). The subsistence meals on both of the Fridays were reasonable considering there was a full day of scientific content. The arrangements for day 1 for 2011 regarding subsistence were acceptable and appropriate when considering sponsorship of the 2012 event.

On day 2 (Saturday) in 2011, lunch was provided following a half day of scientific content and the meeting closed at 1.30pm. A similar format was used in 2012. Allergan submitted that the arrangements presented for 2011 for day 2 regarding subsistence were acceptable and appropriate when considering sponsorship of the 2012 event.

Neither the golf nor the gala dinner were part of the ISU meeting which concluded at midday. The ISU had confirmed that both the golf and gala dinner occurred after the scientific meeting had ended. Delegates who wished to play golf or attend the gala dinner paid their own costs and Allergan had no involvement in any part of these post-meeting activities.

Regarding the request for copies of the invitation, agenda, programme and any other materials, Allergan did not receive any of the documentation for the 2012 meeting as explained above. It did not select or pay for any health professional to attend the meeting.

Allergan understood the initial impression given by the meeting might cause concern. However, it hoped that the above information provided assurance that Allergan provided appropriate sponsorship, in line with the Code. Allergan understood that when sponsoring a meeting it needed to take into account the suitability of all the arrangements, in line with Clause 19.1. This was outlined in its standard operating procedures (SOPs).

The venue was considered to be acceptable, it was chosen by the ISU and met the logistical requirements of the delegates. The subsistence meals provided throughout the one and a half day meeting were appropriate given the length and scientific content of the meeting.

The golf and gala dinner were not part of the meeting. Allergan did not sponsor either of these activities.

In summary, Allergan submitted that it supported a high calibre, independently organised meeting in an acceptable venue and did not fund any social or sporting events. Therefore, it did not believe it had breached Clauses 19.1, 9.1 or 2.

In response to a request for further information Allergan explained that it was fairly new to the field of urology. In 2011 Allergan did not have any products licensed in the UK in this field although it anticipated a licence extension in quarter three or four of 2012 for Botox (botulinum toxin type A) for the management of urinary incontinence in adults with neurogenic detrusor overactivity. At the end of September 2012 Allergan received a UK licence for Botox for the management of urinary incontinence in adults with neurogenic detrusor overactivity due to subcervical spinal cord injury (traumatic or non-traumatic) or multiple sclerosis, who were not adequately managed with anticholinergics; patients should be already catheterising or willing and able to catheterise if required. Therefore, when the RCSI contacted the company about the meeting it did not wish to be an exhibitor as it had no product to promote.

However, it was happy to consider supporting the ISU Annual Meeting. The meeting was of an extremely high educational standard with a full programme of scientific sessions, guest lectures and a moderated poster session with top experts in the field of urology. Therefore, the RCSI was advised to complete an Allergan Sponsorship/Donation Request form and it selected the option 'Meeting Attendance'.

The request for support for the meeting was reviewed and approved as a sponsorship request. Allergan did not want to be an exhibitor at the meeting but was happy to provide support towards venue hire and AV costs. The letter that was sent to the RCSI detailed the terms of the support. Allergan requested that the following statement be added to all the associated materials produced in relation to the event.

'An educational grant was provided by Allergan Ltd to the Irish Society of Urology to support this independent course. Allergan has had no involvement in the logistics, design or content of the course.'

Whilst the request selected 'Meeting Attendance' (in error), Allergan clarified the terms of its support ie, via an educational grant, rather than as an exhibitor. Allergan did not have an exhibition stand at the meeting.

Only a regional scientific services (RSS) manager from Allergan attended the meeting. Allergan submitted that this was a non-promotional role and the RSS manager was present in a non-promotional capacity to attend the scientific sessions and meet with top experts in the field of urology. No Allergan employees attended the conference dinner on Friday, 21 September 2012.

Allergan did not complete an exhibitor registration form.

**PANEL RULING IN CASE AUTH/2547/11/12**

In addition to its general comments set out above, the Panel noted that Allergan had not had an exhibition stand at the meeting and its support was for the venue hire and AV costs. The company had clearly stated its terms of support in a letter to the RCSI.

The Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Allergan's submission regarding the conference facilities offered by the venue but considered that other non-luxurious venues would have had adequate conference facilities. The Panel further noted that Allergan's SOP stated that in general a 4 star rating would be the top level of hotel to be selected as a venue.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. The penultimate page of the programme referred to the educational grant provided by Allergan. It was for the same amount as that paid for an exhibition stand. There was no indication that the majority of companies listed on the back page had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Allergan in breach of Clause 9.1.

The Panel noted that Allergan had not sponsored any health professional to attend the meeting by paying for accommodation, subsistence or registration fees. The company had supported the venue hire and AV

costs of the meeting. The Panel considered that the venue was on the limits of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its ruling above and the submission that Allergan had not paid for delegates to attend the golf or gala dinner. It decided that the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

**CASE AUTH/2548/11/12 BAXTER**

**RESPONSE**

Baxter stated that its Irish operation was conducted by an Ireland registered branch of Baxter Healthcare Limited based in Dublin, the general manager of which reported directly to the UK general manager.

Baxter was committed to ensuring all its interactions with health professionals and medical institutions were appropriate. In order to achieve this, it had an international policy to regulate all such activities and ensure that requests were reviewed and approved to the relevant local standards. It also regularly reviewed compliance at senior management team meetings.

As was common practice in the industry, Baxter was keen to support and attend scientific events where the attendees were an appropriate and a relevant audience for the company to promote its products. In this case, the ISU was a *bona fide* medical society which held an educational meeting which was CPD accredited. The policies that covered the hospitality Baxter staff could give and receive were followed in the approval of this meeting (and in the attendance and conduct of employees at this meeting). However, this complaint highlighted an important issue for all companies, which was that it had limited influence over the organisation of and advertising for meetings run by medical societies. Yet the perception resulting from additional activities and the presentation of the meeting could be damaging.

Baxter submitted that it had not breached Clauses 19.1, 9.1 or 2 as it did not offer any hospitality to the delegates and its contribution was simply to support a scientifically valid event in the provision of an exhibition stand.

This complaint had made Baxter aware of how a sponsor could be perceived as having a broader involvement in an event than was actually the case. Consequently employees involved with the approval of events were re-trained to ensure everyone was aware of this issue and that Baxter took steps to ensure the boundaries of its involvement were clear to everyone who attended the meetings it supported.

While Baxter included and referred to the letter received from the Immediate Past President of the ISU, the company neither agreed with nor endorsed the sentiments expressed about the nature of the complaint.

Baxter stated that the meeting was first discussed in November 2011, before the organiser sent details of the meeting to Baxter, as a possible opportunity to inform Irish urologists about Baxter products. In April 2012 the Baxter office in Dublin received a letter from the ISU/RCSI which offered the opportunity to hire an exhibition stand at the meeting. Both organisations had their headquarters in Dublin and were well regarded and established medical societies. The invitation requested a fee of €1,850 to cover the cost of the stand itself, access to the exhibition area and scientific sessions for company attendees, plus lunch and tea/coffee for company attendees throughout each day of the congress. In accordance with Baxter's policy the request was reviewed by the Dublin office and approved.

Further, a formal agreement between Baxter Healthcare Limited and the RCSI set out which specific event Baxter was supporting, the value of Baxter's contribution, and what Baxter would receive in return. Namely, the right to have a stand for the duration of the scientific meeting; to secure space for a satellite symposium; to present the company logo to the delegates and to be named as a sponsor of the event in any associated communications.

Baxter stated that it never offered or committed to sponsoring any of the hospitality associated with the meeting and no Baxter employee was present during any hospitality event. The company's involvement was solely to be present during the scientific meeting in order to present and promote products to relevant delegates.

The meeting agenda referred to a gala dinner and golf being available but this was after the close of the scientific meeting. As reflected in the signed agreement between the parties, Baxter had no involvement with the organisation of, sponsoring of, or attendance at the golf and gala dinner that preceded or followed the scientific event. Baxter's employees left the meeting when the scientific sessions closed at 12.30pm and this was the limit of Baxter's involvement.

Since receiving this complaint, Baxter's Dublin office had received unsolicited a letter of clarification dated 5 December from the conference organiser, the Immediate Past President of ISU about the hospitality offered at the meeting, particularly the social activities. The intention of the letter was to clarify the role of the companies involved in the conduct of the meeting. In the clarification, the Immediate Past President emphasised the Society's independence in selecting the venue and also noted that no company had ever influenced the choice of venue for this annual meeting. According to the Immediate Past President the gala dinner took place at Stormont, the venue was made available to the society by [a politician] and all attendees paid for their own meals, and any other associated costs.

Baxter submitted that it did not offer any hospitality to the delegates; the agreement between the two organisations referred solely to Baxter's financial contribution to sponsor the exhibition stand and the lunch and refreshments provided during the scientific

meeting. None of Baxter's contributions were made for hospitality and no Baxter employee was present or involved in the hospitality provided, specifically the golf and gala dinner. Therefore, there had been no breach of Clause 19.1.

As there was no evidence to support a breach of Clause 19.1 there was likewise no evidence to support a breach of Clauses 9.1 or 2.

Baxter concluded that it had not identified any breach of internal policy or process. The clearly stated limitation on its involvement in the signed agreement showed no involvement in the hospitality beyond that associated with the scientific sessions. It had found no evidence of failure on the part of its processes. Baxter provided copies of its relevant policies.

Despite Baxter acting within its processes and the Code, the final agenda for the event, as supplied by the organisers, presented additional activities outside of the meeting in a way that could have implied inappropriate sponsorship. To ensure Baxter was alert to this risk and to avoid this situation in the future, all Baxter employees involved in the approval of events would be retrained to ensure they were made aware of, and took action to avoid, this issue in future. In addition, Baxter would review its contract template to strengthen how its involvement in an event was made clear to everyone who attended the meetings it supported and it would not sponsor any meetings or congress where there could be the perception of excessive hospitality, even if Baxter had nothing to do with the provision or sponsorship of such activities.

In response to a request for further information, Baxter confirmed that it did not hold a satellite symposium at this meeting. A standard agreement template was used by the Ireland team and they omitted to remove this section from the template. Training for the Ireland sales and marketing team was organized for January 2013 and this would include a refresher on using templates.

The first Baxter UK heard of the meeting was when it received notification from the Authority.

Baxter stated that it received an initial email from the organizing secretary around March 2012 announcing this meeting. Baxter's email policy resulted in the automatic deletion of emails after a fixed period of time and the relevant employee no longer had the email.

A copy of the exhibitor registration form was provided. Baxter submitted that this showed that it did not intend to be involved in the dinner or any social event. The costs of accommodation at the venue were within the normal range and did not raise any concern. No Baxter representative attended the conference dinner.

**PANEL RULING IN CASE AUTH/2548/11/12**

In addition to its general comments set out above, the Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It considered that other non-luxurious venues would have had adequate conference facilities. The Panel further noted that Baxter's SOP stated that hotels must be modest and suited for business purposes. Generally this included 4 star business or similarly situated hotels. Higher class hotels might be selected only when there were legitimate and documented reasons. Examples were given.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Baxter UK in breach of Clause 9.1.

The Panel noted that Baxter had not sponsored any health professional to attend the meeting by paying accommodation, subsistence or registration fees. The company had only paid for an exhibition stand. The Panel considered that the venue was on the limits of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its rulings above and the submission that Baxter had not paid for delegates to attend the golf or gala dinner. It decided that the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

**CASE AUTH/2552/11/12 FERRING**

**RESPONSE**

Ferring Pharmaceuticals (UK) Ltd contacted colleagues in Ferring Ireland for confirmation of the details. Ferring Pharmaceuticals (Ireland) Ltd was a wholly owned subsidiary of Ferring BV in the Netherlands. Ferring Ireland did not report into Ferring Pharmaceuticals (UK) Ltd, although both companies were part of the Ferring Group.

Ferring submitted that the ISU was a 32 county, all Ireland medical body that represented medical professionals involved in urology in Ireland. The ISU, part of the Royal College of Surgeons in Ireland (RCSI) and based in Dublin, was a renowned professional society that arranged high calibre annual scientific meetings.

The President of the ISU confirmed to Ferring that the ISU independently chose the venue for the meeting. Neither Ferring Ireland, nor any other pharmaceutical company, had any control or influence over the choice of location or venue. The venue had excellent conference facilities. Ferring UK did not believe that a

5 star rating, or the presence of a spa, represented an incentive for delegates to attend the conference, as many hotels that had previously been to be shown acceptable had similar facilities. In addition, delegates paid their own expenses to attend the meeting.

The ISU independently developed the meeting programme and decided on all arrangements for the meeting with no influence from Ferring Ireland, or any other pharmaceutical company. The scientific programme clearly showed that the educational content was of the highest quality.

Ferring Ireland telephoned a manager in Ferring UK to let him/her know that the ISU meeting would take place in Belfast in September 2012. The UK manager decided that this was specifically an ISU meeting, that it was therefore outside of the remit of the UK company and that Ferring UK would not provide any sponsorship, nor be involved in the meeting in any way.

Ferring Ireland's sponsorship of this meeting was limited solely to paying to be an exhibitor. Ferring Ireland participated in the trade exhibition to allow the ISU members from the Republic of Ireland to discuss the latest information on Ferring products with Irish health professionals. No hospitality, gifts or promotional aids such as pens were available at the Ferring Ireland stand, or at the meeting.

The President of the ISU chose to hold the gala dinner at Stormont, which was made available by a politician.

No member of Ferring Ireland played golf or used the spa at the meeting. Ferring Ireland had no influence on any of the ISU arrangements, including transport for golf on the Saturday afternoon or the gala dinner. The Ferring Ireland exhibition stand closed as the scientific programme ended at lunch time on the Saturday.

Ferring Ireland did not pay for, or select, any medical professional to attend the meeting, made no additional arrangements with delegates before the meeting or provide any additional hospitality.

The Immediate Past President of the ISU confirmed in writing that no pharmaceutical company had any hand, act or part in any of the issues raised by the anonymous complainants, and that Ferring Ireland, and other pharmaceutical companies, had merely exhibited at this scientific meeting. As Ferring Ireland did not provide or facilitate any hospitality at this meeting, the question of the level of subsistence was not relevant. The Immediate Past President of the ISU also confirmed that all delegates were responsible for all their own expenses during the meeting, including registration fees, meals, accommodation and golf, for which the ISU made arrangements for those delegates who wished to play at their own expense at the conclusion of the scientific programme, at a course that was located several miles from the meeting venue.

A copy of the scientific programme for the meeting was provided. No invitations were sent out by Ferring Ireland, nor was any information sent out to delegates.

In light of the information provided, Ferring UK did not believe that breaches of Clauses 19.1, 9.1, or 2 could be ruled. Ferring UK was not involved in any way in this meeting, and Ferring Ireland did not provide, or facilitate any hospitality. All delegates who attended this independently organised, well regarded, professional scientific meeting were responsible for all own expenses. Ferring Ireland attended the meeting solely in the capacity of a trade exhibitor and acted in a professional manner, maintaining high standards of conduct.

In response to a request for further information, Ferring confirmed that there was no correspondence between Ferring Ireland and the ISU and/or the RCSI in relation to the meeting in question other than the exhibitor registration form. This was an important scientific meeting that Ferring Ireland was well aware of and since no other support was to be offered, there was no need for any additional correspondence.

Ferring Ireland purchased two tickets for the conference dinner that was held on Friday, 21 September, but these were subsequently not used by any Ferring employee and nor were not passed on to anyone else. Ferring Ireland also purchased a ticket for the gala dinner held on Saturday, 22 September. A Ferring Ireland employee attended the dinner as a mark of respect for the ISU and its President. He had confirmed that he did not buy any drinks at the dinner. Ferring Ireland did not sponsor any guests to attend the gala dinner or sponsor any part of the function.

**PANEL RULING IN CASE AUTH/2552/11/12**

In addition to its general comments set out above, the Panel noted Ferring UK's submission and considered that Ferring Ireland should know that any meeting which it sponsored in Northern Ireland was covered by the UK Code. This was clearly set out in the supplementary information to Clause 1.8 of the ABPI Code and reflected requirements in the EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals.

The Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Ferring UK's submission regarding the conference facilities offered by the venue but considered that other non-luxurious venues would have had adequate conference facilities.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements

for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Ferring UK in breach of Clause 9.1.

The Panel noted that Ferring had not sponsored any health professional to attend the meeting by paying accommodation, subsistence or registration fees. The Panel considered that the venue was on the limit of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that Ferring's involvement went further than paying for a trade exhibition. One employee had attended the gala dinner.

The Panel considered that purchasing a ticket for the gala dinner was inappropriate. Although health professionals paid for their own tickets it was not acceptable for a company to be involved in such an event. The educational content of that day (3 hours 40 minutes in the morning) did not justify the gala dinner in the evening which appeared to be a social event. A breach of Clause 19.1 was ruled. High standards had not been met in this regard and a further breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its rulings above and the submissions that Ferring had not paid for delegates to attend the golf or gala dinner. It decided that, on balance, the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

**CASE AUTH/2554/11/12 IPSEN**

**RESPONSE**

Ipsen Limited stated that it was extremely dismayed to receive the complaint about the ISU meeting. Ipsen Pharmaceuticals, named as one of the sponsors of the meeting, was the Irish operating company; Ipsen Limited was the UK operating company. Ipsen Limited took responsibility for this meeting as it was held in the UK.

The meeting was an annual academic event which attracted urological surgeons primarily from the Republic of Ireland, with smaller delegations from Northern Ireland and the UK mainland. The statistics for participants were provided.

On 18 May 2012 Ipsen was invited to complete the exhibitor booking form in order to have a stand at the meeting. In June 2012 an email exchange between the Irish and UK operating companies confirmed that, since the meeting was in Belfast, ABPI compliant stands and materials would be required, and also that the stand would be managed by one representative from the UK and two from the Irish company. It was agreed that the cost of the stand would be split 1:2 with the UK reimbursing the Irish company for one third of the total cost of €1,850.

On 3 July 2012 a senior product manager reviewed the preliminary details of the meeting as per the current local SOP. At that time, the only details from ISU were the dates, venue and the fact that the meeting was organised by the ISU which Ipsen knew was a well-respected, academic association based in the Irish Republic but which described itself as an all island society.

Ipsen stated that this situation was very common when conference organisers initially approached companies about stand space and sponsorship. The venue had already been selected by the ISU and, while possibly at the limits of acceptability for ABPI Code compliance, it was a very well-known conference venue with the capacity to cope with a moderately sized meeting both in conference rooms and overnight accommodation, and was extremely well situated to suit the delegates travelling from the Republic, Northern Ireland and the UK as it was close to major road networks, Belfast City airport and the docks. This meeting was known to be an important event for the Irish urological community and it would have been the scientific programme and not the venue which was the main attraction. The meeting was therefore 'approved' with the proviso that there were no major sporting/leisure activities occurring at the same time and that the programme was of a scientific nature.

On 29 August 2012 the UK office received the final agenda for the meeting which confirmed the scientific nature of the meeting.

Ipsen did not advertise the meeting or produce any materials specific to the meeting and it did not sponsor any delegates to attend. Ipsen did not provide any sponsorship beyond the cost of the stand: its sponsorship in this regard was acknowledged on the last page of the programme. Both the stand and materials on it were already certified for use under the ABPI Code. Ipsen representatives did not attend the conference dinner on Friday night [see below]. All Ipsen representatives (and, in fact, the representatives from the other companies present) left at the end of the scientific meeting, defined clearly in the programme as 12.10pm on Saturday ('Lunch & Close of Meeting' in the 'programme at a glance' and 'Close of Meeting – Lunch and Exhibition' on the detailed agenda). The stand was dismantled late morning and was collected between 1–1.15pm. The impression to the delegates attending the meeting would have supported the scientific meeting ending at lunchtime as the company stands were packed up, collected and company staff left. Ipsen had no part in the organisation or sponsorship of either the golf or the gala dinner which were paid for separately from the meeting by the delegates themselves. Ipsen received an unsolicited letter from the ISU in December 2012 confirming this and the fact that the golf was arranged for a time after the scientific meeting had ended.

In response to the specific points raised by the Authority, Ipsen submitted that it had demonstrated that it had sponsored a stand at the meeting (jointly shared by the Irish and UK affiliates and with UK-appropriate materials) with no other sponsorship provided to either the ISU or any individual delegates; the venue was acceptable based on the geography of the delegates attending and was a known conference venue; the ISU was a well-respected academic

institution and the final programme for the meeting reflected the high quality of the clinical programme and posters presented; the scientific meeting clearly ended at lunchtime on Saturday and this was obvious from the programme provided to delegates by ISU; no pharmaceutical company had any part in the after-meeting arrangements. Thus Ipsen did not believe that it was in breach of Clauses 19.1 or Clause 2.

Ipsen followed its own SOPs and believed that the scientific meeting arrangements, venue and hospitality were appropriate to the nature of the meeting and the delegates attending. With hindsight, the wording of the programme was perhaps not ideal as the sponsors were listed after the end of Saturday's events (including the after-meeting events) and not after the end of the scientific meeting which would have more accurately reflected Ipsen's involvement. It was possible that it could have written to the ISU after it received the final programme at the end of August to ask it to clarify this and amend the programme accordingly, but Ipsen did not, which was regrettable but not, it submitted, a failure to maintain high standards and it was not, therefore, in breach of Clause 9.1.

In response to a request for further information, Ipsen provided a copy of the exhibitor registration form. It confirmed that two Ipsen representatives from the Irish affiliate attended both the meeting and the dinner. Ipsen apologised that this was not known when it first responded. The managing director of the Irish affiliate had only been told on 7 January that the two Irish affiliate representatives had attended. Ipsen did not consider that this materially changed any of the points in its original response as the conference dinner was an integral part of the scientific congress.

**PANEL RULING IN CASE AUTH/2554/11/12**

In addition to its general comments set out above, the Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Ipsen UK's submission regarding the conference facilities offered by the venue but considered that other non-luxurious venues would have had adequate conference facilities. The Panel further noted that Ipsen's SOP on regional, national and international sponsored meetings clearly stated that it was not acceptable to use 5 star hotels.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Ipsen UK in breach of Clause 9.1.

The Panel noted that Ipsen had not sponsored any health professional to attend the meeting by paying accommodation, subsistence or registration fees. The Panel considered that the venue was on the limit of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its rulings above and the submissions that Ipsen had not paid for delegates to attend the golf or gala dinner. It decided that the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

The Panel noted that two Ipsen representatives had attended the conference dinner. The Panel was concerned that Ipsen's initial response stated that its representatives had not attended the conference dinner. This was unacceptable; self regulation relied upon a full and frank disclosure of the facts at the outset. Noting all the circumstances, the Panel decided to take no further action.

**CASE AUTH/2556/11/12 JANSSEN**

**RESPONSE**

Janssen stated that it had conducted a review of the circumstances surrounding the provision of support to this meeting. The one and a half day meeting had a rigorous scientific content, with over 9 hours of lectures and other presentations on relevant medical and scientific issues.

Janssen's office in Ireland agreed to sponsor the 2012 meeting following an email exchange with the RCSI, which organised the ISU meeting. Copies of the emails were provided. When Janssen internally approved the meeting for sponsorship, it knew the timing and venue of the meeting and a 'save the date' flyer was available but there was no agenda or 'welcome message' from the ISU President for that year's meeting available, although a copy of the agenda for the 2011 ISU meeting was provided to Janssen to assist in its decision-making.

The ISU had confirmed that payment of €1,850 for an exhibition stand represented approximately 2% of the total cost of the meeting and therefore, with 19 sponsoring companies, the industry sponsorship for the meeting accounted for less than 50% of the total cost. On the basis of the above information, Janssen Ireland approved the meeting, which it considered complied with its own SOP and Clauses 16.1, 16.3, 16.4 and 16.6 of the IPHA Code of Practice.

No Janssen materials for health professionals were produced for this meeting and the exhibition stand displayed a previously approved, non-promotional, Janssen corporate banner. Two Janssen staff attended the scientific meeting, largely for their own personal education in the field of prostate cancer, but left at the close of the scientific programme and before the optional golf and gala dinner on 22 September 2012.

Although the meeting was held in Northern Ireland and attended by UK health professionals, the relevant staff in the Republic of Ireland approved the event in the same way as if it were to be held in the Republic of Ireland and did not refer the meeting to the UK office for consideration under the ABPI Code.

No health professionals, either based in the Republic of Ireland or the UK, were sponsored by Janssen to attend the meeting.

Janssen stated that although the hotel chosen by the ISU for the meeting was described as a 5 star venue, it also had dedicated conference facilities and was conveniently situated with regards to road and air links. The features of the hotel were not portrayed as an attraction to potential delegates in the information provided to Janssen at the time of approval or in the subsequent 2012 scientific programme brochure provided to health professionals who expressed an interest in attending. The room and breakfast rates offered to delegates, £120 to £150 per night, fell within Janssen's internal travel policy limits and were not excessive. The hotel amenities did not include a golf course.

Janssen noted that on the basis of the known 2011 meeting and confirmed in the 2012 scientific programme, the planned meeting had a rigorous scientific content. The ISU (founded in 1956) was a well established and respected learned society. Attendance at the 2012 meeting would have earned eligible health professionals 9 CPD points from the RCSI. In the opinion of the approving Janssen staff in Ireland, the educational value of the meeting, rather than its venue or associated social activities, would have been the overriding attraction for delegates.

Janssen submitted that although it appeared on the agenda, golf took place after the scientific meeting had closed. A letter from the then President of the ISU stated that the golf was arranged for a time after the scientific meeting had finished and when the trade exhibitors and indeed some attendees had already left. The ISU confirmed that the pharmaceutical companies' sponsorship was not used to pay for golf, and Janssen had been informed by the ISU that delegates were expected to pay for this activity themselves. No Janssen staff attended the golf, which was played on a golf course close to, but not part of, the hotel complex, and no support was provided by Janssen for any individual health professionals to play golf.

Janssen stated that as specified in the scientific programme, the gala dinner at the Northern Ireland Parliament Building at Stormont was sponsored by a politician in the Northern Ireland government. The ISU had informed Janssen that pharmaceutical sponsorship money was not used to fund the gala dinner. The current President confirmed in a letter to Janssen's Acting Head of Medical Affairs in Ireland that it had always been procedure at the ISU meetings that any social activities available to delegates, accommodation and travel expenses were funded by themselves. No Janssen employee attended the dinner, and no support was provided by Janssen for any individual health professionals to attend the event.

In considering the complaint, Janssen addressed the three clauses of the Code. The meeting had a clear and robust educational content and the non-educational content, such as optional golf and the gala dinner, was secondary to this and was not, in Janssen's opinion, the major attraction of this meeting to delegates. As mentioned above, Janssen did not sponsor any individual health professional to attend the meeting. Although the reference to a gala dinner and golf in the scientific programme brochure was unfortunate in the context of appropriateness under the Code, the organisers confirmed that financial support received from Janssen and other sponsors did not fund or subsidise these activities. Given the size of the meeting (132 delegates) and considerations of convenience and actual cost of rooms, the ISU's choice of venue could be seen to be justifiable and not inappropriate in the circumstances. In light of the information provided above, Janssen submitted that no breach of Clause 19.1 had occurred.

The review and approval of sponsorship was done according to the relevant Janssen SOP and appropriate permissions were sought. In this regard, Janssen submitted that high standards were maintained from a company perspective. The failure to review the meeting using the ABPI Code as well as the IPHA Code to a meeting organised by an all Ireland learned society held in Northern Ireland was a regrettable oversight by the Janssen staff in Ireland. As high standards were maintained, albeit without the ABPI Code being used as the standard by which the meeting was judged, Janssen submitted that no breach of Clause 9.1 had occurred.

Given the above, Janssen submitted that its support of this scientific meeting it had not brought the pharmaceutical industry into disrepute, so no breach of Clause 2 had occurred.

In response to a request for further information Janssen stated that its stand consisted of two Janssen corporate banners. Available on the stand were a reprint of a journal article, a corporate-branded blank notebook and a corporate-branded ballpoint pen. (Copies of the banners, a copy of the reprint and photographs of the notebook and pen were provided). The items were provided under the provisions of Clause 14.1 of the IPHA Code.

The stand was manned by a manager from Janssen's Irish office, who also attended some of the scientific sessions. The other Janssen staff member who attended from the Irish office, did not man the stand but attended the scientific sessions. The majority of the combined time of the two Janssen employees at the conference was spent attending the scientific sessions. Both attended the conference dinner.

Janssen noted that the ticket which it purchased for the gala dinner was not used. To confirm the information in its initial response, no Janssen employee attended the gala dinner and no health professional was given this unused ticket, nor sponsored to attend.

The draft agenda was available on 27 July 2012 and a final agenda available on 27 August 2012. Janssen received these documents on or near these dates.

**PANEL RULING IN CASE AUTH/2556/11/12**

In addition to its general comments set out above, the Panel noted Janssen UK's submission and considered that the Irish affiliate should know that any meeting which it sponsored in Northern Ireland was covered by the UK Code. This was clearly set out in the supplementary information to Clause 1.8 of the ABPI Code and reflected requirements in the EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals.

The Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Janssen UK's submission regarding the conference facilities offered by the venue but considered that other non-luxurious venues would have had adequate conference facilities. The Panel noted that Janssen's SOP stated that venues should be modest and appropriate.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Janssen UK in breach of Clause 9.1.

The Panel noted that Janssen had not sponsored any health professional to attend the meeting by paying accommodation, subsistence or registration fees. The Panel considered that the venue was on the limit of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that Janssen's involvement went further than paying for a trade exhibition. A ticket had been purchased for the gala dinner which the Panel considered was inappropriate. Although health professionals paid for their own tickets it was not acceptable for a company to be involved in such an event. The educational content of that day (3 hours 40 minutes in the morning) did not justify the gala dinner in the evening which appeared to be a social event. The Panel noted that no-one from Janssen used the dinner ticket but considered that its purchase showed an intent to attend. A breach of Clause 19.1 was ruled. High standards had not been met in this regard and a further breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its rulings above and the submissions that Janssen had not paid for delegates to attend the golf or gala dinner. It decided that, on balance, the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

The Panel noted that Janssen did not attend the meeting solely in the capacity of a trade exhibitor. Janssen had purchased a ticket for the gala dinner although this ticket was not used. The Panel was very concerned that this information had not been provided with Janssen's initial response. This was unacceptable; self regulation relied upon a full and frank disclosure of the facts at the outset.

**CASE AUTH/2559/11/12 ORION**

**RESPONSE**

Orion Pharma UK contacted Orion Pharma (Ireland) Ltd for confirmation of the details. Orion Pharma (Ireland) Ltd was a wholly owned subsidiary of Orion Corporation in Finland and operated in Ireland independently of Orion Pharma (UK) Ltd.

The ISU was based in Dublin. It was an 'all Ireland' medical body that represented medical professionals involved in urology and was part of the RCSI based in Dublin. It was a renowned professional society that arranged high calibre, annual scientific meetings.

The President of the ISU confirmed that the society independently chose the venue for the meeting. Orion Pharma Ireland did not have any control or influence over the choice of venue.

Orion submitted that the venue provided high quality conference facilities, it was centrally located with excellent transport connections and was not lavish, extravagant or deluxe. The travel industry site 'Travel Weekly', which was widely respected, rated the hotel as 'Superior First Class'. Orion did not believe that a 5 star rating, or the presence of a spa, represented an incentive for delegates to attend the conference. Many hotels that had previously been considered to be acceptable under the Code had similar facilities. In addition, individual delegates were personally responsible for meeting their own costs and expenses associated with their attendance at this meeting.

The ISU developed the programme and the arrangements for the meeting independently of all pharmaceutical companies, including Orion Pharma Ireland. The scientific programme established that the educational content of the meeting was of the highest value, demonstrating a clear, high calibre educational content with presentations and posters covering aspects of urology ranging from basic science to practical surgical matters delivered by Irish, UK and international experts.

Sponsorship by Orion Pharma Ireland was limited to a payment to the ISU for the sole purpose of registering as a trade exhibitor at the meeting. Orion Pharma Ireland participated in the trade exhibition solely to engage with members of the ISU from the Republic of Ireland. All Orion Pharma Ireland personnel left the congress at lunchtime on Saturday 22 September, at the conclusion of the scientific programme.
The President of the ISU chose to hold the gala dinner at Stormont, which was made available to the society by [a named politician]. No pharmaceutical companies had any input into this event. Orion Pharma Ireland did not make any financial

contribution to this portion of the event and Orion UK understood that all attendees paid for their meals and all other costs associated with the gala dinner.

No member of Orion Pharma Ireland attended the gala dinner, played golf or used the spa at the meeting. Orion Pharma Ireland had no influence on any of the ISU arrangements, including transport for golf or the gala dinner.

Orion Pharma Ireland did not pay for, or invite, any medical professionals to attend this meeting and made no additional arrangements with delegates prior to the meeting, or provide any additional hospitality during the event.

A letter sent to Orion Pharma Ireland by the President of the ISU confirmed that no pharmaceutical company had any hand, act or part in any of the issues raised in the anonymous letter of complaint, and that Orion Pharma Ireland, and the other pharmaceutical companies, were merely exhibitors at this scientific meeting.

As Orion Pharma Ireland did not provide or facilitate any hospitality at this meeting, the question of the level of subsistence was not relevant. The President of the ISU had also confirmed that all delegates were responsible for all their own expenses during the meeting, including registration fees, meals, accommodation and golf. The ISU made arrangements for those delegates who wished to play golf, at their own expense, at the conclusion of the scientific programme.

Orion UK did not provide any sponsorship and was not involved in the meeting in any way.

In view of the information provided, Orion UK did not believe that breaches of Clauses 19.1, 9.1 or 2 could be ruled. Orion Pharma UK was not involved in any way in this meeting, and Orion Pharma Ireland did not provide, or facilitate any hospitality. All delegates attending this independently organised, well regarded, professional scientific meeting were responsible for meeting all their own expenses. Orion Pharma Ireland attended the meeting solely as a trade exhibitor and acted in a professional manner, maintaining high standards of conduct.

In response to a request for further information, Orion Pharma UK confirmed that three Orion Ireland personnel attended the conference dinner on and that no employees from Orion Ireland attended the gala dinner.

A copy of the completed exhibitor registration form was provided.

Orion Pharma Ireland received an email link to the draft programme on 30 July 2012, with the final programme being requested from the organisers on 18 September 2012.

**PANEL RULING IN CASE AUTH/2559/11/12**

In addition to its general comments set out above, the Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Orion UK's submission regarding the conference facilities offered by the venue but considered that other non-luxurious venues would have had adequate conference facilities.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Orion UK in breach of Clause 9.1.

The Panel noted that Orion UK had not sponsored any health professional to attend the meeting by paying accommodation, subsistence or registration fees. The Panel considered that the venue was on the limit of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its ruling above and the submission that Orion had not paid for delegates to attend the golf or gala dinner. It decided that the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

**CASE AUTH/2560/11/12 PFIZER**

**RESPONSE**

Pfizer stated that the ISU was a society that promoted the specialty of urology and its related medical sciences in Ireland. The society was advisory to the Irish Department of Health and Joint Committee on Higher Surgical Training (JCHST) for UK & Ireland and had historically included health professionals from Northern and Southern Ireland. Pfizer Ireland was approached in February 2012 and again in May 2012 to take an exhibition stand during the scientific meeting exhibition times. Nineteen pharmaceutical and medical device companies exhibited at this meeting. There were no attendees from Pfizer UK and one representative from Pfizer Ireland at the meeting. No health professionals were sponsored to attend by Pfizer Ireland or Pfizer UK. Pfizer Ireland asked Pfizer UK to provide two exhibition stands.

Pfizer Ireland reviewed the request in line with its local procedure. The totality of the event was looked at and a number of factors including the number of exhibitors, the CPD accreditation and scientific programme were considered. Pfizer Ireland asked the meeting organisers how the Pfizer funding would be allocated and how the social elements of the meeting would be funded. A comprehensive response from

the ISU in this regard was received which confirmed that the financial contribution provided by Pfizer would be allocated to the scientific programme only and was a nominal sponsorship amount (2%) in relation to the overall cost of the meeting.

The following information was sent by the ISU by email on 30 August 2012:

'This sponsorship provides the opportunity for Pfizer Healthcare and other colleagues from the pharmaceutical and medical equipment industries to promote their products and services to delegates. The sponsorship received from exhibitors assists with the overall costs involved in hosting the meeting including, the design and printing costs associated with the scientific programme, the audio-visual equipment hired for presentations and delegate day rates @ £45 each which covers tea/coffee breaks and lunch per day. We anticipate 100 – 120 delegates will attend this year's meeting. The sponsorship received from exhibitors does not assist with the expenses of the social functions including the golf, conference dinner and gala dinner or accommodation. Guests are responsible for purchasing tickets to each social event. To do this delegates register online, when registering they are also given the option to reserve tickets for the social events, if they wish to attend. Ticket prices cover the costs associated with each event (including transport and wine). We also offer the option to companies to specifically sponsor a social function or contribute towards a speaker's travel costs. Only in this instance is sponsorship used for a social event. The income produced through delegates' registrations covers the majority of the expenditure. The sponsorship of €1,850.00 accumulates 2% of the total cost of the meeting.'

Pfizer Ireland did not receive or request any further information in this regard, and agreed to the minimum level of sponsorship which only covered the educational content of the congress.

Pfizer provided a copy of a letter received from the Immediate Past President of the ISU which clarified the respective roles of the ISU and the pharmaceutical companies in the meeting arrangements.

As per the ISU email of 30 August, payment for the exhibition stand did not contribute towards any of the social events related to the meeting. This would have only occurred if the company had specifically chosen to sponsor one of these events, which it did not.

Pfizer Ireland procedure outlined the process that should be followed in managing any corporate sponsorship activity. In circumstances where Pfizer Ireland considered sponsorship of a third party event, regardless of whether the meeting was taking place in another country, this was the process that applied. In this instance Pfizer Ireland followed the process. Approval was obtained electronically based on the information submitted. As there were no UK based individuals on the steering committee of the ISU (which received the corporate sponsorship) and no UK health professionals sponsored to attend, the Irish SOP did not require approval of the meeting arrangements from the UK. This was an oversight and the Irish SOP was being revised with immediate effect to ensure that if an Irish meeting took place in Northern Ireland then ABPI Code approval would be sought for the arrangements of the meeting.

Pfizer did not have any involvement or engage directly with any meeting delegates; information was sent directly by the ISU. Pfizer did not produce or supply any materials about the meeting arrangements that were directly provided to delegates. Nor did Pfizer (UK or Ireland) sponsor any health professionals to attend.

Pfizer accepted that due to the nature of the venue and the potential perception of the social aspects described on the agenda, it was not appropriate to provide sponsorship by taking up the offer to have an exhibition stand at the meeting. The internal processes in place within Pfizer Ireland were followed and the request was assessed in line with the Irish SOP and approved accordingly. In light of the issues that had arisen Pfizer UK was working with colleagues in Pfizer Ireland to revise the procedure to be applied in circumstances where they were invited to exhibit at meetings to be held in Northern Ireland. Pfizer accepted that a breach of Clause 19.1 had occurred.

Pfizer accepted that high standards had not been maintained and a breach of Clause 9.1 had occurred.

Pfizer's submitted that its contribution to the overall expense of this meeting represented 2% of the overall costs involved and its presence was limited to a small exhibition area, with one Pfizer Ireland employee in attendance. Pfizer provided the minimum level of sponsorship on the basis that this supported the educational activities of the meeting only. Pfizer did not sponsor any of the social aspects of the meeting, nor did its sponsorship support excessive hospitality as alleged. It did not sponsor any UK or Irish health professionals to attend and there were no Pfizer UK staff at the meeting. Pfizer strongly believed that the industry had not been brought into disrepute by sponsorship of the educational content only for a third party meeting run by the ISU and therefore no breach of Clause 2 had occurred.

In response to a request for further information, Pfizer stated that following on from a previous request from the RCSI for participation in the meeting, Pfizer Ireland called the RCSI to request additional detail on how the exhibition stand fee of €1,850 would be allocated and also to request confirmation of the ISU council members for internal approval purposes.

Pfizer Ireland confirmed its attendance on 31 August and returned the exhibitor registration form on 3 September. When the registration form was completed the Pfizer Ireland manager had not decided who and how many would attend from Pfizer Ireland. Of the three names entered on the form Pfizer Ireland confirmed that only one attended: Pfizer Ireland received from RCSI a draft agenda on 30 July. No Pfizer Ireland employee attended the conference dinner.

**PANEL RULING IN CASE AUTH/2560/11/12**

In addition to its general comments set out above, the Panel noted Pfizer UK's submission that its Irish SOP did not require UK approval for this meeting. The Panel considered that the Irish affiliate should know that any meeting which it sponsored in Northern Ireland was covered by the UK Code. This was clearly set out in the supplementary information to Clause 1.8 of the ABPI Code and reflected requirements in the EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals. The Panel noted that Pfizer UK had taken action to prevent such an oversight happening again.

The Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Pfizer UK's submission that it was not appropriate to provide sponsorship given the nature of the venue and what it described as the social aspects stated on the agenda. The Panel considered that other non-luxurious venues would have had adequate conference facilities.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Pfizer UK in breach of Clause 9.1 as acknowledged by the company.

The Panel noted that Pfizer had not sponsored any health professional to attend the meeting by paying accommodation, subsistence or registration fees. The Panel considered that the venue was on the limit of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its rulings above and the submission that Pfizer had not paid for delegates to attend the golf or gala dinner. It decided that the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

**CASE AUTH/2561/11/12 RECORDATI**

**RESPONSE**

Recordati Pharmaceuticals Ltd confirmed that the response from Recordati Ireland Ltd be used as the formal response to this complaint.

No-one attended the ISU Annual Meeting from Recordati Pharmaceuticals Ltd. Recordati Ireland Ltd did attend this meeting. This was a completely separate business to the UK subsidiary and was not connected in any way to the UK business.

In Ireland, the pharmaceutical industry had its own code of practice, the IPHA Code of Marketing Practice. Recordati Ireland submitted that it took the IPHA Code seriously and every effort was made to ensure that it was always fully compliant. Recordati Ireland submitted that it was certainly 100% compliant at the ISU Annual Meeting.

Recordati Ireland provided a letter from the Immediate Past President of the ISU together with the breakdown of the number of attendees who attended the meeting from Northern Ireland, Republic of Ireland and overseas which addressed the clear inaccuracy of the first point of the complaint.

Recordati Ireland understood that the ISU had already sent a similar letter to the PMCPA to address several other inaccuracies in the complaint. Recordati Ireland was sure that the correspondence would also clarify fully how and by whom the meeting was organised.

Recordati Ireland noted a number of points from the letter from the ISU. These being: firstly, that it did not have any input in choosing the venue for the meeting or gala dinner. Secondly, no-one from Recordati Ireland attended the gala dinner and thirdly, Recordati Ireland did not have any input into arranging/paying for golf for any delegates. None of the Recordati Ireland employees played golf at this meeting.

Recordati Ireland was invited to exhibit at the trade exhibition during the course of the meeting and a separate room was provided by the ISU for this purpose. Recordati Ireland had no part to play in the organisation or running of this meeting.

Recordati Ireland asked the PMCPA to confirm in writing to Recordati Pharmaceuticals Ltd that as it was not at the meeting in question, Case AUTH/2561/11/12 was closed. It also asked the PMCPA to confirm that it was happy with the clarification regarding Recordati Ireland's exemplary conduct at the meeting.

In response to a request for further information, Recordati Ireland provided a copy of the exhibitor registration form which was completed and returned to the ISU on 21 May 2012. Four Recordati Ireland employees attended the conference dinner.

Recordati Ireland did not sponsor any health professional to attend any part of this meeting or to attend either of the two dinners. Recordati Ireland was provided with a link to the programme on 27 August.

**PANEL RULING IN CASE AUTH/2561/11/12**

In addition to its general comments set out above, the Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Recordati UK's submission regarding the conference facilities offered by the venue but considered that other non-luxurious venues would have had adequate conference facilities.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Recordati UK in breach of Clause 9.1.

The Panel noted that Recordati had not sponsored any health professional to attend the meeting by paying accommodation, subsistence or registration fees. The Panel considered that the venue was on the limit of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its ruling above and the submission that Recordati had not paid for delegates to attend the golf or gala dinner. It decided that the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

**CASE AUTH/2563/11/12 TAKEDA**

**RESPONSE**

Takeda UK was very concerned to hear of this complaint and took the allegations very seriously.

The sponsorship was arranged by Takeda Products Ireland Ltd, the Irish operating company. Takeda UK Ltd was not previously aware of this activity but took responsibility as this meeting was held in the UK.

Takeda Products Ireland paid €1,850 to have a promotional stand within the exhibition area at the meeting. The stand was staffed by three employees from Takeda Products Ireland across the two days. Two members of staff were present on the stand and the conference dinner on Friday and were joined by a third member of staff on the stand for the morning of the second day. These three employees were present on the stand until lunchtime on the second day when the meeting ended and the stand was taken down. This was the limit of their involvement and they were not present at the golf or the gala dinner, both of which took place at other venues and after the educational meeting closed.

Takeda Products Ireland Ltd did not know about the golf arranged by the ISU to take place after the end of the meeting. Takeda Products Ireland first received a confirmation email from the ISU on 30 July 2012 in which there was a link to the draft agenda. This email was sent to an administrative member of staff within Takeda Products Ireland who had been the contact for the meeting in terms of the financial arrangements. The link no longer worked and so Takeda UK was unable to check the draft programme made available at that time. However, it had been confirmed that no-one within Takeda Products Ireland was aware of the golf arranged to take place at a local golf course separate to the hotel after the meeting. When this email was received by the operations assistant it was seen purely as a confirmation of the booking made for the stand space at the meeting.

Takeda Products Ireland had no involvement in inviting any delegates to the meeting and as such did not have any materials or invitations relating to this meeting. Takeda Products Ireland did not select or pay for or support any health professional to attend any aspect of the meeting.

The meeting was not arranged by Takeda Products Ireland, it solely paid for commercial stand space and promotional attendance at the trade exhibition at the meeting. The involvement of Takeda Products Ireland was noted at the back of the final programme provided to delegates.

This meeting had a clear and full educational programme and hence it was this educational content which attracted the delegates to the meeting and not the venue.

The meeting was an independent meeting organised by the ISU. The ISU described itself as an all island society and as such delegates might come from both the Republic of Ireland and Northern Ireland and on this occasion the meeting was held in Belfast. The educational meeting was held in high regard and indeed the President's message of welcome in the final programme commented on the number of scientific abstracts that could not be accommodated which confirmed that the scientific profile of the meeting was of a high standard. Health professionals attending this high quality event were awarded a certificate for 9 hours of CPD. The first day of the meeting was from 9am until 5pm followed by a council meeting and then the conference dinner held in the hotel. On the second day the meeting started at 8.30am and closed at 12.10pm at which point the three employees from Takeda Products Ireland left.

The content of the meeting was wholly selected and organised by the ISU without input from Takeda. Takeda Products Ireland was invited to have a stand within the trade exhibition. When Takeda Products Ireland agreed to this it knew the meeting venue but not the planned programme or the planned golf and gala dinner. When the booking form was completed the gala dinner was noted on the form but Takeda Products Ireland did not book places to attend.

Clause 19 stated that meeting venues must be appropriate and companies must not sponsor or organize entertainment. Takeda Products Ireland played no part in the selection of the venue as this was selected by the meeting organisers. However, Takeda UK considered that the venue, although a 5 star hotel, could be acceptable because it was a well used conference venue with adequate rooms for the number of delegates (132 health professionals plus meeting organsiers, speakers etc) and conveniently located for transport links. The hotel's website stated that it was located close to Belfast city centre and Belfast City Airport and so it provided very good access for the delegates from across Ireland. The

hotel had eight conference suites and 500 complimentary car parking spaces and so could cater for large events such as this meeting.

The hotel did not have a golf course. The final programme showed that neither the golf nor the gala dinner were part of the educational meeting; both events took place after the meeting had closed. The gala dinner was sponsored by a named politician as stated in the programme. Takeda Products Ireland did not sponsor either event. The meals during the meeting were taken in the hotel and were not paid for or organized by Takeda. On the basis of the points detailed above Takeda refuted the alleged breach of Clause 19.1.

The payment of space for a promotional stand at the trade exhibition area of this meeting was approved by Takeda Products Ireland according to its SOP. As such Takeda UK refuted the alleged breach of Clause 9.1. It strongly refuted any allegation that this activity constituted a breach of Clause 2 which was a sign of particular censure and reserved for such circumstances. This was an isolated incident where someone had agreed and paid a small fee to have a promotional stand at a trade exhibition at an educational meeting. When it agreed to have the stand at the meeting Takeda Products Ireland was not provided with the full agenda and so did not know that the organisers would arrange for golf and a gala dinner after the close of the meeting. The gala dinner after the second day of the meeting was known to Takeda Products Ireland when it completed the booking form, but at this time there was still no mention of golf.

The draft programme was first provided to Takeda Products Ireland on 30 July 2012. An email was provided in which it could be seen that the draft programme was available by a website link. Unfortunately the link no longer worked and Takeda UK was now unable to check what aspects of the programme could be reviewed at this time. Members of the sales and marketing department reviewed the meeting venue in line with their SOP when approving support for the meeting by way of a promotional stand. When they approved this activity they did not know about the golf.

The meeting organisers had written to Takeda unsolicited upon hearing about the complaint. Takeda assumed that one of the other companies which was also subject to a complaint regarding the meeting brought the matter to the ISU's attention. A copy of the letter received on 5 December by Takeda Products Ireland was provided. This stated the ISU's position.

**PANEL RULING IN CASE AUTH/2563/11/12**

In addition to its general comments set out above, the Panel noted that the venue was a 5 star conference hotel and would thus be seen as luxurious. In that regard the Panel queried whether the venue met the requirements of the Code. It noted Takeda UK's submission regarding the conference facilities offered by the venue but considered that other non-luxurious venues would have had adequate conference facilities.

Taking all the circumstances into account it appeared that the pharmaceutical companies listed on the back page of the programme had supported all the arrangements for the two-day meeting held at a luxurious venue with golf and a gala dinner. There was no indication that the majority of companies listed had only paid to exhibit at the meeting. The conference programme stated that without participation from the pharmaceutical and medical equipment industries the meeting would not be possible. The Panel considered that the arrangements for the meeting as described in the programme and the impression given were unacceptable. In this regard, high standards had not been met. The Panel ruled Takeda UK in breach of Clause 9.1.

The Panel noted that Takeda UK had not sponsored any health professional to attend the meeting by paying accommodation, subsistence or registration fees. The Panel considered that the venue was on the limit of acceptability given its 5 star rating but nonetheless ruled no breach of Clause 19.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel noted its ruling above and the submission that Takeda had not paid for delegates to attend the golf or gala dinner. It decided that the circumstances did not warrant such a ruling and no breach of Clause 2 was ruled.

**Complaint received** **4 December 2012**

**Cases completed:**

**Case AUTH/2546/11/12** **7 February 2013**
**Case AUTH/2547/11/12** **12 February 2013**
**Case AUTH/2548/11/12** **12 February 2013**
**Case AUTH/2552/11/12** **14 February 2013**
**Case AUTH/2554/11/12** **12 February 2013**
**Case AUTH/2556/11/12** **7 February 2013**
**Case AUTH/2559/11/12** **12 February 2013**
**Case AUTH/2560/11/12** **12 February 2013**
**Case AUTH/2561/11/12** **20 February 2013**
**Case AUTH/2563/11/12** **12 February 2013**

# HEALTH PROFESSIONALS v BOEHRINGER INGELHEIM

## Online survey

**Three complaints were received relating to an on-line survey about stroke prevention in atrial fibrillation. The matter was taken up with Boehringer Ingelheim in the UK as the survey was commissioned by its parent company Boehringer Ingelheim International GmbH. The complainants were a head of medicines management (Case AUTH/2565/11/12), a primary care trust medicines management lead (Case AUTH/2566/11/12) and a general practitioner (Case AUTH/2567/11/12).**

**The complainants had all been invited, by email, to participate in the survey. The selection criteria for the survey as outlined in the invitations included firstly, patients that were previously treatment naïve who had started on therapy (warfarin, Pradaxa (dabigatran) or Xarelto (rivaroxaban, Bayer's product)) in the last three months and secondly patients who were on warfarin, Pradaxa or Xarelto and who switched to a different therapy (warfarin, Pradaxa or Xarelto) in the last three months. The email stated that to complete the study, including two online patient forms, would take around 60 minutes and an honorarium of £70 was offered.**

**The complainant in Case AUTH/2565/11/12 was concerned at the possibility of a £5 payment for switching to a certain branded medicine.**

**The complainant in Case AUTH/2566/11/12 alleged that the survey was in breach of the Code and noted that he/she was not a member of the healthcare advisory board referred to in the email.**

**The complainant in Case AUTH/2567/11/12 queried whether the email complied with the Code or study methodology.**

**The detailed response from Boehringer Ingelheim is given below.**

**The Panel considered that the rulings set out below applied equally to all three complaints.**

**The Panel noted it was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code. The survey had been used in the UK and therefore it came within the scope of the UK Code.**

**The only requirement in the Code that specifically mentioned market research stated that, *inter alia*, such activities must not be disguised promotion. They must be conducted with a primarily scientific or educational purpose. The supplementary information referred to the British Healthcare Business Intelligence Association (BHBIA) Legal and Ethical Guidelines for Healthcare Market Research. The Panel noted that market research had to be conducted for a *bona fide* purpose. If market research was ruled to be disguised promotion, any payment was also likely to be in breach. A company should be mindful of the impression created by the invitation to participate in the survey and description therein of any payment.**

**The Panel noted that, to help it develop its business strategy, Boehringer Ingelheim GmbH had commissioned a third party to conduct an international survey about prescribing practices. The survey was conducted from July to December 2012. The third party subcontracted another company to conduct the UK fieldwork and this organisation had, itself, subcontracted another company to recruit by telephone. It was an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf. Thus Boehringer Ingelheim was responsible for the activities of the third party and all those subcontracted.**

**The Panel noted that the request for proposal document sent by Boehringer Ingelheim referred to a general market research plan which was likely to lead to a series of market research studies.**

**The Panel noted that at the formal kick off meeting about the survey between the third party and its subcontractor in September 2012, project objectives and survey administration details (programming) were discussed by telephone and were not documented in writing. The hard copy version of the survey provided by Boehringer Ingelheim included programming and other instructions. There was no written instruction about how the survey should be communicated to potential participants.**

**The invitation was written and approved by the company subcontracted by the third party. The Panel was concerned about the lack of input and/or approval by Boehringer Ingelheim of the invitation. In the Panel's view Boehringer Ingelheim should have, at the very least, satisfied itself that the invitations were not promotional.**

**The Panel noted that the survey itself was detailed and included screening questions about participants' roles and activities. There were detailed questions about non-valvular atrial fibrillation (NVAF) and treatment with Pradaxa and Xarelto. After completing general questions, participants were asked about a specific patient. The Panel considered that the survey focussed on the condition and general requirements about treatment. It did not focus on Boehringer Ingelheim's product.**

**The Panel noted that whilst the £70 payment, for completion of the survey and two patient forms, did not seem unreasonable given the submission that**

**the estimated time for completion was 60 minutes, the Panel was nonetheless concerned about the description of the payments in the email invitations.**

**The emails in Cases AUTH/2565/11/12 and AUTH/2566/11/12 were very similar but all three were different to that provided by Boehringer Ingelheim which did not have 'GBP' inserted both in the subject and email heading, and did not refer to the provision of gift vouchers. Gift vouchers were referred to in the email in question in Case AUTH/2567/11/12. The Panel made its rulings on the invitations provided by the complainants.**

**The email invitations in Cases AUTH/2565/11/12 and AUTH/2566/11/12 were very similar. They referred to the recipients' membership of a healthcare advisory board. The subject heading read 'Earn 70 GBP GBP honorarium: Stoke Prevention' and the invitation was headed 'Online study for 70 GBP'. Participants were asked to complete the survey and a minimum of two and a maximum of 10 patient forms. Additional honoraria of £15 were offered per additional patient form completed. Participants were '… incentivized with an extra hono of 5 GBP for each Switched to Pradaxa or Switched to Xarelto PRFs [patient record forms] completed'.**

**The email in question in Case AUTH/2567/11/12 was similar. The email bore a different subject heading '[details of the subcontractor] Online Study on Stroke Prevention in Non-Vascular Fibrilation'. There was no reference to membership of an advisory board. The payment was described as 'a £70 cheque or a £70 Amazon.co.uk gift certificate'. This invitation did not make it clear that the maximum of 10 patient record forms included the 2 completed within the main survey. In addition the ordering of paragraphs was such that three paragraphs detailing payments appeared at the beginning of the email before the patient selection criteria whereas in the emails to the other complainants and that provided by Boehringer Ingelheim the order was reversed. This email also included '… incentivized with an extra hono of 5 GBP for each Switched to Pradaxa or Switched to Xarelto PRFs completed'.**

**The Panel queried whether the disproportionate emphasis on payment in all the emails was appropriate given the need to ensure that the material was non-promotional. Both the subject title and email heading referred to the £70 honoraria in Cases AUTH/2565/11/12 and AUTH/2566/11/12 and in addition throughout the invitations at issue in Cases AUTH/2565/11/12 and AUTH/2567/11/12 all references to honoraria were emboldened and, in the Panel's view, were designed to catch the reader's eye.**

**The Panel was concerned that an additional £5 incentive was offered for each form for patients who had been switched to Pradaxa or Xarelto. The Panel noted Boehringer Ingelheim's submission that the numbers of such patients in the UK was small and thus payment of the incentive would aid collection of data in these patient types. It further submitted that the overall payment was reasonable. The Panel considered that offering an extra payment for identifying certain patients in a market research study was not necessarily a breach of the Code providing there was a *bona fide* need for such data, the overall payment was reasonable and the overall arrangements including the description of the payment did not render the arrangements promotional.**

**The Panel noted that the survey was retrospective but there was a small theoretical possibility that health professionals could switch patients on learning that an extra £5 would be paid. In order to do this Boehringer Ingelheim submitted that prescribers would need to recall patients to an anticoagulant service, explain details of the switch and obtain agreement to switch. There would need to be sufficient time for each patient's warfarin to be stopped and their blood clotting rate rechecked until it reached a certain level before they could be started on Pradaxa. The doctor would then have to complete the survey. The Panel noted that the emails in Cases AUTH/2565/11/12 and AUTH/2566/11/12 clearly referred to the survey being on patients that the doctor had seen in the last three months. This was mentioned three times and underlined in these emails before the statement 'On top of that you'll be incentivized with an extra hono[rarium] of 5GBP for each Switched to Pradaxa or Switched to Xarelto PRFs completed'.**

**The email in Case AUTH/2567/11/12 was slightly different. The emboldened sentence 'On top of that you will be incentivized with an extra hono[rarium] of £5 for each Switched to Pradaxa or Switched to Xarelto PRFs completed' gave more visual emphasis to the incentivisation payment. Whilst noting that the first paragraph referred to participating in 'an online study on The Stroke Prevention in Non Valvular Atrial Fibrillation treated in the last 3 months' this sentence was not grammatically correct. Towards the end of the email a description of the patient selection criteria included the statement 'in the last 3 months' twice.**

**The Panel was concerned that the reference to the 'Switched to Pradaxa' or 'Switched to Xarelto PRFs' might be seen as offering a payment for switching. In this regard it was particularly concerned about the email in Case AUTH/2567/11/12. It queried whether such an offer would be an inducement to prescribe which was prohibited under the Code.**

**Taking all the circumstances into account, the Panel did not consider that the survey itself was promotional and thus it could not be argued that its nature in this regard was disguised. No breach was ruled. Similarly, and noting its finding that the survey was non-promotional the Panel did not consider that the level of payment was inappropriate, nor given the retrospective nature of the study that the level of payment otherwise amounted to an inducement to prescribe, no breach was ruled on these narrow points.**

**The Panel was, however, very concerned about the disproportionate emphasis on payment in the subject title and body of the emails as described above. In addition, the reference to the incentivized payments was a standard paragraph which in Case AUTH/2567/11/12 was emboldened. A reader**

**glancing at the email might get the impression that a £5 honorarium was payable in relation to each patient switched to Pradaxa or Xarelto. Indeed this was the complainant's impression in Case AUTH/2565/11/12. Such an impression was unacceptable. The Panel was also concerned about the apparent lack of control exercised over the content of the invitations. High standards had not been maintained and a breach was ruled.**

**Noting its rulings above and on balance, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.**

The Authority received three complaints relating to an on-line survey about stroke prevention in atrial fibrillation. Following contact with the market research company which emailed details of the survey the matter was taken up with Boehringer Ingelheim Limited in the UK as the survey was commissioned by its overseas parent company Boehringer Ingelheim International GmbH. The complainants were a head of medicines management (Case AUTH/2565/11/12), a quality and medicines management lead at a primary care trust (PCT) (Case AUTH/2566/11/12) and a general practitioner (Case AUTH/2567/11/12).

The complainants had all been invited, by email, to participate in the survey which was about patients with non-valvular atrial fibrillation. The selection criteria for the survey as outlined in the invitations were firstly, patients that were previously treatment naïve who had started on therapy (warfarin, Pradaxa (dabigatran) or Xarelto (rivaroxaban, Bayer's product)) in the last three months; secondly patients who were on warfarin, Pradaxa or Xarelto and who switched to a different therapy (warfarin, Pradaxa or Xarelto) in the last three months; thirdly, that patients should not be enrolled in a clinical trial. The email stated that to complete the study, including two online patient forms, would take around 60 minutes for which an honorarium of £70 was offered.

Pradaxa was indicated for primary prevention of venous thromboembolic events in adults who had undergone elective total hip replacement surgery or total knee replacement surgery. It was also indicated for prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (NVAF) with one or more of certain risk factors.

Xarelto 10mg was indicated for the prevention of venous thromboembolism (VTE) in adults undergoing elective hip or knee replacement surgery. Xarelto 15mg and 20mg were indicated to prevent stroke and systemic embolism in adults with NVAF with one or more named risk factors. It was also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of DVT and PE in adults.

**Case AUTH/2565/11/12**

**COMPLAINT**

The complainant was concerned at the possibility of a £5 payment for switching to a certain branded medicine.

**Case AUTH/2566/11/12**

**COMPLAINT**

The complainant alleged that the survey was in breach of Clause 18.1 and noted that he/she was not a member of the healthcare advisory board referred to in the email.

**Case AUTH/2567/11/12**

**COMPLAINT**

The complainant, who had discussed the survey with his local pharmaceutical advisor and a partner in the practice who was a prescribing lead for a primary care trust (PCT), queried whether the email, which was sent to his/her practice, complied with the Code or study methodology.

When writing to Boehringer Ingelheim, the Authority asked it to respond to each complaint in relation to Clauses 2, 9.1, 12.2 and 18.1.

**RESPONSE**

Boehringer Ingelheim submitted that the market research survey in question was commissioned by Boehringer Ingelheim Headquarters, Boehringer Ingelheim International GmbH, as a global project that was conducted from July to December 2012 in Germany, the US, Canada, Spain, Japan, Brazil and the UK.

Boehringer Ingelheim GmbH noted that the basis for the three complaints related to disguised promotion of a medicine and the attempt to induce, or inducement of, physicians to switch to a particular medicine. However, the invitation to the market research survey, and the survey itself, requested only retrospective information, ie, information relating to past prescribing practices of physicians invited to participate. Thus, no physicians were induced or incentivised to prescribe any patients a particular medicine as a consequence of the survey. Accordingly, Boehringer Ingelheim considered that there had been no breach of the Code.

Boehringer Ingelheim explained that Boehringer Ingelheim GmbH commissioned a third party agency to conduct the market research survey in question as part of a commercial assessment relating to prescribing practices, in order to help Boehringer Ingelheim GmbH develop its business strategy for Pradaxa. The survey was developed by the third party in response to Boehringer Ingelheim GmbH's request for proposal, and was described in the project proposal. The survey was subsequently approved by Boehringer Ingelheim GmbH. Boehringer Ingelheim GmbH and the third party had a master services agreement in place under which the market research work was governed. The third party subcontracted another company to conduct the fieldwork for this market research project. There was no direct contract between Boehringer Ingelheim GmbH and the company subcontracted by the third party. The company subcontracted by the third party did not know Boehringer Ingelheim GmbH was the project sponsor (as per standard policy) until the

PMCPA disclosure. Copies of Boehringer Ingelheim GmbH's request for proposal, the third party's corresponding project proposal, and relevant master services agreements and contracts were provided.

The company subcontracted by the third party created the invitation letter and reimbursement structure, and used the invitation to recruit physician respondents from its healthcare advisory board. As members of the British Healthcare Business Intelligence Association (BHBIA) the subcontracted company conducted market research in the UK in accordance with the BHBIA Legal and Ethical Guidelines for Healthcare Market Research, October 2011; the company confirmed that all staff working on this survey had completed BHBIA training.

Boehringer Ingelheim referred to Section 8 of the BHBIA guidelines which set out the key principles and guidelines relating to the recruitment and reimbursement of market research participants. Boehringer Ingelheim submitted that the invitation emailed to potential participants incorporated all the elements required to comply with the BHBIA guidelines including clear, unambiguous information about the research study, information about what exactly their participation would entail, together with a direct statement about the reimbursement offered.

Boehringer Ingelheim GmbH submitted that the honorarium offered for completion of the survey fell within the BHBIA's definition of market research 'reimbursement', which stated that to encourage participation in a market research study reimbursement should be: kept to a minimum level; proportionate to the amount of time involved and appropriate to the respondent type and the nature of the task(s).

Boehringer Ingelheim GmbH was confident that the wording of the invitation and the survey was sufficiently clear that the questions asked related only to past prescribing practices finished at the time of the interview and therefore would not have induced any participant to prescribe a particular medicine.

Boehringer Ingelheim explained that the survey was conducted to help understand the prescribing drivers for physicians in terms of NVAF anticoagulant treatment. In July 2012, Boehringer Ingelheim GmbH's Pradaxa global brand team identified a number of key business questions about the NVAF market and Pradaxa in particular that needed to be answered for brand planning. In essence, these questions centred around understanding more about physicians' decision making in the NVAF market, how this had evolved, how the new oral anticoagulant class and individual products were being perceived, and how that perception was likely to further evolve with increasing competition within the market.

No target lists of physicians were used in the UK. Neither Boehringer Ingelheim GmbH nor the third party identified any lists of physicians for the purposes of recruiting specific target physicians in the UK. The subcontracted company had an existing group of UK health professionals, the healthcare advisory board, which was used together with some supplemental telephone recruiting. This meant physicians who might not be on the advisory board were recruited and proactively provided their email to receive study invitations. There was not a separate invitation for these physicians.

No physician-identifying information of any kind was provided to Boehringer Ingelheim GmbH.

The survey asked participants to recall their decisions to change people between medicines in the previous 3 months. After entering the survey, via the link on the invitation letter, the participants were asked 'Doctor, you previously stated that you can recall information about at least one NVAF patient of the following patient types and that you have treated the following number of NVAF patients in the last 3 months'. Once survey respondents agreed that they could recall such patients, they were asked to complete the survey based on memory of a patient (no identifiers were requested nor opportunities given to provide such identifying information).

The healthcare advisory board was comprised of physicians and other health professionals who shared their opinions and views on a variety of health issues by participating in opinion surveys delivered via a variety of channels, including the Internet.

Boehringer Ingelheim explained that the company subcontracted by the third party had recruited respondents using many different recruitment sources and methodologies including special recruitment campaigns or techniques and offline methods for physicians or healthcare practitioners in hard-to-reach geographical locations. Examples were provided.

When respondents were recruited to the healthcare advisory board, it was made very clear that they had joined an opinion survey community and that they would be asked periodically to participate in online research. They were also given a link to terms and conditions when they registered and had to actively agree to abide by these before participating. A link to the subcontracted company's privacy policy was referenced on the registration page and on the terms and condition page for each study.

All recruited members had completed a 'double' opt-in process. After registration, each new member received a confirmation email which described community membership and provided instructions for continuing membership as well as the option to opt-out.

Boehringer Ingelheim submitted that 34 physicians received the honorarium with additional incentive for completing recall charts for patients they saw in the past 3 months who were moved from one medicine to another. There were 54 recall charts for which this additional honorarium was paid. The maximum number of patient charts that could be completed within the survey was 10; and so the maximum amount of additional reimbursement for

these 10 charts for information about patients previously switched to Pradaxa or Xarelto would be £50.

Boehringer Ingelheim noted that the survey did not ask for patients to be switched from one therapy to another. Switching patients was not Boehringer Ingelheim GmbH's intent; on the contrary the objective was to understand why patients might have been switched in the past. The additional £5 for the information on a concluded switch to Pradaxa or Xarelto was intended to be paid to learn more about the motivation of the health professional and the circumstances of the case, but not to induce any switch – indeed, this would not be possible because the switch had already been completed.

Boehringer Ingelheim GmbH believed that the invitation letter clearly inquired about the past actions of the physicians invited to participate in the survey. The survey (including the invitation at issue) asked about prescribing decisions that were made within the three months before the invitation was sent. In that regard Boehringer Ingelheim noted that the phrase 'the last 3 months' was used three times in the invitation letter and was emboldened and underlined to emphasise that the information sought related to patients that had already been switched independently of the study. The additional honorarium offered as reimbursement for information was to be provided to respondents only in respect of information they provided about prescribing decisions made in the three months preceding the date of the survey request. It was neither the company's intention nor its expectation that any patients were switched by prescribers as a result of this survey, and to its knowledge that was the case.

In summary, Boehringer Ingelheim GmbH did not intentionally attempt or design the survey to induce or incentivise any physician to prescribe Pradaxa, nor switch patients to Pradaxa. In addition the objective of the survey was not intended to be disguised promotion in any way. Indeed, the three most commonly prescribed oral anticoagulants in the UK (warfarin, Xarelto and Pradaxa) were all mentioned equally in the invitation. Furthermore, the PMCPA's letter with details of the complainants' declarations of interest revealed that at least one of the complainants 'had no idea' which company was involved. This disclosure would therefore call into question the assertion that this market research survey was disguised promotion. The objective of the survey was to seek further information about the factors that drove physicians to make the decisions about prescribing oral anticoagulants.

Boehringer Ingelheim acknowledged the complainants' concerns, but it appeared that they might have misinterpreted the purpose of the study based on the wording of the invitation. Boehringer Ingelheim GmbH believed that the wording of the invitation letter was clear that additional honorarium was to be provided to respondents only in respect of information relating to prescribing decisions made in the three months before the survey request. In addition, the enclosed documentation indicated that Boehringer Ingelheim GmbH's objective for this market research was not to induce or incentivise the prescribing of Pradaxa; nor was it to use the market research as disguised promotion. However, Boehringer Ingelheim GmbH submitted that it would invest additional efforts in future to ensure that the risk of similar misinterpretation of its market research materials would not occur again.

In conclusion, Boehringer Ingelheim GmbH did not believe that the conduct of the market research study in question was in breach of Clauses 2, 9.1, 12.2 and 18.1. The company refuted any allegations of misconduct made by the complainants and believed that the evidence provided demonstrated that high standards in relation to healthcare market research had been maintained.

In response to a request for further information, Boehringer Ingelheim clarified that the market research survey was part of a wider market research project and commercial assessment commissioned by Boehringer Ingelheim International GmbH in order to help develop its business strategy for Pradaxa.

Boehringer Ingelheim submitted that a briefing was provided during a formal kick off call between the third party and the company subcontracted by the third party in September 2012. Project objectives and survey administration details were discussed by telephone and were not documented in writing. A copy of the survey, which included the programming instructions given by the third party to its subcontractor, as well as the survey objectives were provided.

While the subcontracted company carried out the survey in the UK it, in turn, subcontracted another company to do some additional telephone recruiting using the same script (see below). This company was a member BHBIA and all team members had successfully completed their BHBIA training before conducting any telephone recruiting for this survey.

Boehringer Ingelheim noted that Clause 12.2 referred, *inter alia*, to market research activities and stated that these must be conducted with a primarily scientific or educational purpose. Boehringer Ingelheim considered that market research was different from these other activities since it was not inherently clinically scientific or educational. Nonetheless, the purpose of this market research survey was scientific and educational, albeit from a business intelligence analysis perspective rather than a clinical perspective: to help Boehringer Ingelheim GmbH to understand the factors that drove physicians to make prescribing decisions in the treatment of NVAF.

The Boehringer Ingelheim GmbH request for proposal document described the five key questions that the Pradaxa Global team wanted to answer to help develop its 2013 marketing strategy. This market research project was commissioned to help Boehringer Ingelheim GmbH answer these questions, which underpinned the objectives of the wider market research project, of which this survey was one workstream.

Boehringer Ingelheim submitted that in all market research studies, many of those invited to participate did not respond and when it was believed that it would be harder to meet quotas needed for testing significance in the sample, then an additional honorarium might be used as a way to gain additional responses. For example:

- When conducting qualitative or quantitative market research with several physician specialties, it might be challenging to meet the minimum required sample of a particular specialty. Increasing honoraria to that specialty group for participation (of course staying within fair market value) might be acceptable.

- When conducting quantitative market research and one patient type or target sample quota was lagging, adding an additional honorarium to get closer to the required response for statistical analysis for that segment was a standard practice (again, staying within reasonable fair market value).

This approach was in line with the BHBIA Legal & Ethical Guidelines for Healthcare Market Research:

' 8.26 If there is evidence to suggest that the standard reimbursement will not be successful, e.g. if past experience proves that a respondent type is particularly difficult to recruit because they belong to an exceptionally small universe; then it is possible to amend the reimbursement but it should not be excessive in relation to the task(s) required.'

Boehringer Ingelheim stated that all patient types were of equal importance in this survey. The reality was that the new oral anticoagulants (Pradaxa and Xarelto) were in the UK market for significantly less time than in other countries (due to a later launch date in the UK) and hence the potential numbers of such patients were relatively small and such patients were harder to locate. Therefore, the idea of the additional £5 honoraria was implemented to encourage physicians who had already made the prescribing decision and had such a patient to provide recall information for that type of patient (instead of, or in addition to other patient types they could provide information for).

Specifically, an additional £5 honorarium was offered for the patients switched from warfarin to Pradaxa or Xarelto within the last 3 months to aid the collection of these patient types as it was anticipated that they would be limited in number.

In summary Boehringer Ingelheim submitted that increasing honoraria, within fair market value, was a standard market research tool to reach meaningful quota of responses within a survey. No quota in this survey was deemed 'more valuable' (nor was that atypical in market research). The additional honorarium offered was to increase the likelihood of achieving an adequate number of samples for more difficult quota areas and not to influence prescribing practice.

Boehringer Ingelheim stated that in order for health professionals 'to read the email invitation, switch patients then complete the survey' as suggested by the PMCPA, they would first need to recall patients to an anticoagulant service, explain the details of the switch and obtain each patient's agreement to be switched. There would then need to be sufficient time for each patient's warfarin to be stopped and each patient's International Normalised Ratio (INR) [measurement of time for blood to clot compared to an average] to be rechecked until it fell below 2.0, before he/she could be started on Pradaxa.

The market survey in question was only available for clinicians in the UK to complete from 19 October to 1 December 2012 and so any health professionals switching patients from warfarin to Xarelto or Pradaxa would only be able to do so between those two dates. Given the detailed process described above, Boehringer Ingelheim believed it would be extremely unlikely for this type of switch to happen especially given that the only reimbursement for such a switch would be a maximum additional sum of £50 (if 10 patients had been switched from warfarin to Pradaxa or Xarelto).

Boehringer Ingelheim stated that if Boehringer Ingelheim GmbH's intended to incentivise health professionals to switch patients to Pradaxa as alleged, then it would be illogical and counterproductive to offer the same additional honorarium for switches to another company's product, Xarelto. The intentions of this Boehringer Ingelheim GmbH market research survey and the wording of the invitation email were never for health professionals to switch patients to Pradaxa based on this survey.

Boehringer Ingelheim submitted that 111 UK physicians participated in the survey, and no UK specific conclusions were drawn in the resulting market research report (as this was a global project being run in several countries). Instead, the general report was used to educate Boehringer Ingelheim about prescribers' decision-making process and thus helped to inform the Boehringer Ingelheim GmbH global marketing strategy for the coming year. Boehringer Ingelheim noted that the request for proposal from Boehringer Ingelheim GmbH was for the wider global market research project as a whole rather than for just the survey in question.

Boehringer Ingelheim submitted that the healthcare advisory board was not a Boehringer Ingelheim initiative. It was an initiative of the company subcontracted by the third party and was accessible only to that company and its affiliates and no other third parties. Physicians did not receive any fees or honoraria payments just for subscribing to the healthcare advisory board. Honoraria payment was provided only on completion of online surveys, and only for those for which the health professionals were eligible. There were more than 70,000 members of the healthcare advisory board.

Boehringer Ingelheim stated that 8,917 physicians were contacted by email recruitment via the healthcare advisory board and an additional 1,200

physicians outside of the healthcare advisory board community were emailed to participate. A further 175 physicians outside of the healthcare advisory board community were contacted via telephone to participate in the online survey.

Details of the telephone script that would have been used were provided as follows: GPs would have been offered an honorarium of £70 as per the original email invitation.

> 'Hello Dr .....,
>
> It's ..... calling from [the name of the subcontractor] and we are conducting a 60 minute online study on the **Management and therapy preferences for treatment of Stroke Prevention in Non-Valvular Atrial Fibrillation** with an incentive payment of £100. Is this something that would be of interest?
>
> I do have some questions that I need to ask to make sure that you fit criteria. Are you okay to go through these with me now?.'

Boehringer Ingelheim submitted that it was made aware of the overall global market research project in July 2012 but was not operationally involved; the global project dated from July to December 2012. The survey was one workstream of a global market research project. Work relating to this survey commenced in the UK in October 2012.

Boehringer Ingelheim GmbH considered that the wording of the invitation letter was clear that the additional honorarium was to be provided to survey respondents only in respect of information relating to prescribing decisions made in the three months preceding the date of the survey request. The objectives outlined in the request for proposal indicated that Boehringer Ingelheim GmbH's intention for the wider market research project and the specific study in question was not to induce or incentivise the prescribing of Pradaxa; nor was it to use the market research as disguised promotion. Therefore Boehringer Ingelheim GmbH did not believe that the conduct of the market research study in question was in breach of Clauses 2, 9.1, 12.2 or 18.1.

**PANEL RULING**

The Panel noted that it had received three separate complaints about the survey and invitations. It considered that the rulings set out below applied equally to all three complaints.

The Panel noted Boehringer Ingelheim's submission that the market research survey in question was commissioned by Boehringer Ingelheim's overseas headquarters, Boehringer Ingelheim International GmbH. It was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code. The survey had been used in the UK and therefore the survey came within the scope of, and had to comply with, the UK Code.

The Panel noted Boehringer Ingelheim's submission that the survey was in line with the BHBIA Legal and Ethical Guidelines for Healthcare Market Research, October 2011 Edition. The role of the Panel was to consider the complaints in relation to the ABPI Code. It had no role in deciding whether the survey was in line with the BHBIA Guidelines.

The only requirement in the Code that specifically mentioned market research was Clause 12.2 which provided that market research activities, clinical assessments, post-marketing surveillance and experience programmes, post-authorization studies (including those that were retrospective in nature) and the like must not be disguised promotion. They must be conducted with a primarily scientific or educational purpose. The supplementary information to Clause 12.2 referred to the BHBIA Guidelines. The Panel considered that market research had to be conducted for a *bona fide* purpose. If market research was ruled to be disguised promotion contrary to Clause 12.2, any payment was likely to be in breach of Clause 18.1. In addition the company should be mindful of the impression created by the invitation to participate in the survey and description therein of any payment.

The Panel noted Boehringer Ingelheim's submission that Boehringer Ingelheim GmbH had commissioned a third party to conduct the international survey as part of its commercial assessment about prescribing practices to help the company develop its business strategy. The survey was conducted from July to December 2012. The third party engaged another company to conduct the fieldwork for the survey in the UK. In turn this organisation subcontracted another company to do some additional telephone recruiting. It was an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf. Thus Boehringer Ingelheim was responsible for the activities of its third party and all those subcontracted.

The Panel noted that the request for proposal document sent by Boehringer Ingelheim explained that Boehringer Ingelheim needed to answer some very important questions relating to prescribing habits. It referred to a general market research plan which was likely to lead to a series of market research studies.

The Panel noted that a formal kick off meeting about the survey between the third party and its subcontractor took place in September 2012. Project objectives and survey administration details (programming) were discussed over the telephone and were not documented in writing. The hard copy version of the survey provided by Boehringer Ingelheim included programming instructions given by the third party to its subcontractor. The Panel noted that these written instructions contained information on the survey background, objectives, methodology and some general survey notes. There was no written instruction about how the survey should be communicated to potential participants.

Boehringer Ingelheim's response included a letter from the company subcontracted by the third party to the third party which explained that the invitation was written and approved by the company subcontracted by the third party. The Panel was concerned about the lack of input and/or approval by Boehringer Ingelheim of the invitation. In the Panel's view Boehringer Ingelheim should have, at the very least, satisfied itself that the invitations were not promotional.

In Cases AUTH/2565/11/12 and AUTH/2566/11/12 the emails in question had been sent by the company subcontracted by the third party to members of its healthcare advisory board. The complainant in Case AUTH/2566/11/12 stated that he/she was not a member of the healthcare advisory board. Boehringer Ingelheim did not know the identity of the complainant and thus could not comment on this. The email in Case AUTH/2567/11/12 had been sent by another group which appeared to be connected to the company subcontracted by the third party.

The Panel noted that the survey itself was detailed and included screening questions about participants' roles and activities. There were detailed questions about NVAF and treatment with Pradaxa and Xarelto. After completing general questions participants were then asked about a specific patient. The Panel considered that the survey focussed on the condition and general requirements about treatment. It did not focus on Boehringer Ingelheim's product.

The Panel noted that whilst the £70 payment, for completion of the survey and two patient forms, did not seem unreasonable given the submission that the estimated time for completion was 60 minutes, the Panel was nonetheless concerned about the description of the payments in the email invitations.

The emails in Cases AUTH/2565/11/12 and AUTH/2566/11/12 were very similar but all three were different to that provided by Boehringer Ingelheim which did not have 'GBP' inserted both in the subject and email heading, and did not refer to the provision of gift vouchers. Gift vouchers were referred to in the email in question in Case AUTH/2567/11/12. The Panel made its ruling on the invitations provided by the complainants.

The email invitations in Cases AUTH/2565/11/12 and AUTH/2566/11/12 were very similar. They referred to the recipients' membership of a Healthcare Advisory Board. The subject heading read 'Earn 70 GBP GBP honorarium: Stoke Prevention' and the invitation was headed 'Online study for 70 GBP'. Participants were asked to complete the survey and a minimum of two and a maximum of 10 patient forms. Additional honoraria of £15 were offered per additional patient form completed. Participants were '… incentivized with an extra hono of 5 GBP for each Switched to Pradaxa or Switched to Xarelto PRFs [patient record forms] completed'.

The email in question in Case AUTH/2567/11/12 was similar. The email bore a different subject heading '[details of the subcontractor]: Online Study on Stroke Prevention in Non-Vascular Fibrilation'. There was no reference to membership of an advisory board. The payment was described as 'a £70 cheque or a £70 Amazon.co.uk gift certificate'. This invitation did not make it clear that the maximum of 10 patient record forms included the 2 completed within the main survey. In addition the ordering of paragraphs was such that three paragraphs detailing payments appeared at the beginning of the email before the patient selection criteria whereas in the emails to the other complainants and that provided by Boehringer Ingelheim the order was reversed. This email also included '… incentivized with an extra hono of 5 GBP for each Switched to Pradaxa or Switched to Xarelto PRFs completed'.

The Panel queried whether the disproportionate emphasis on payment in all the emails was appropriate given the need to ensure that the material was non-promotional. Both the subject title and email heading referred to the £70 honoraria in Cases AUTH/2565/11/12 and AUTH/2566/11/12 and in addition throughout the invitations at issue in Cases AUTH/2565/11/12 and AUTH/2567/11/12 all references to honoraria were emboldened and, in the Panel's view, were designed to catch the reader's eye.

The Panel was concerned that an additional £5 incentive was offered for each form for patients who had been switched to Pradaxa or Xarelto. The Panel noted Boehringer Ingelheim's submission that the numbers of such patients in the UK was small and thus payment of the incentive would aid collection of data in these patient types. It further submitted that the overall payment was reasonable. The Panel considered that offering an extra payment for identifying certain patients in a market research study was not necessarily a breach of the Code providing there was a *bona fide* need for such data, the overall payment was reasonable and the overall arrangements including the description of the payment did not render the arrangements promotional.

The Panel noted that the survey was retrospective but there was a small theoretical possibility that health professionals could switch patients on learning that an extra £5 would be paid. In order to do this Boehringer Ingelheim submitted that prescribers would need to recall patients to an anticoagulant service, explain details of the switch and obtain agreement to switch. There would need to be sufficient time for each patient's warfarin to be stopped and each patient's INR to be rechecked until it fell below 2 before that patient could be started on Pradaxa. The doctor would then have to complete the survey. The Panel noted that the emails in Cases AUTH/2565/11/12 and AUTH/2566/11/12 clearly referred to the survey being on patients that the doctor had seen in the last three months. This was mentioned three times and underlined in these emails before the statement 'On top of that you'll be incentivized with an extra hono[rarium] of **5GBP** for each Switched to Pradaxa or Switched to Xarelto PRFs completed'.

The email in Case AUTH/2567/11/12 was slightly different. The emboldened sentence **'On top of that you will be incentivized with an extra hono[rarium] of £5 for each Switched to Pradaxa or Switched to**

**Xarelto PRFs completed'** gave more visual emphasis to the incentivisation payment. Whilst noting that the first paragraph referred to participating in 'an **online study on The Stroke Prevention in Non Valvular Atrial Fibrillation treated in the last 3 months'** this sentence was not grammatically correct. Towards the end of the email a description of the patient selection criteria included the statement 'in the last 3 months' twice.

The Panel was concerned that the reference to the 'Switched to Pradaxa' or 'Switched to Xarelto PRFs' might be seen as offering a payment for switching. In this regard it was particularly concerned about the email in Case AUTH/2567/11/12. It queried whether such an offer met the requirements of Clause 18.1 as such a payment would be an inducement to prescribe. Clause 18.1 prohibited inducements to prescribe any medicine. In that regard the Panel did not accept Boehringer Ingelheim's submission that it could not be in breach of Clause 18.1 as the survey paid an extra honorarium for patients switched to a competitor product.

The Panel noted its comments above about the online survey. Taking all the circumstances into account the Panel did not consider that the survey itself was promotional and thus it could not be argued that its nature in this regard was disguised. No breach of Clause 12.2 was ruled. Similarly and noting its finding that the survey was non-promotional the Panel did not consider that the level of payment was inappropriate, nor given the retrospective nature of the study that the level of payment otherwise amounted to an inducement to prescribe, no breach of Clause 18.1 was ruled on these narrow points.

The Panel was, however, very concerned about the disproportionate emphasis on payment in the subject title and body of the emails as described above. In addition, the reference to the incentivized payments was a standard paragraph which in Case AUTH/2567/11/12 was emboldened. A reader glancing at the email might get the impression that a £5 honorarium was payable in relation to each patient switched to Pradaxa or Xarelto. Indeed this was the impression gained by the complainant in Case AUTH/2565/11/12. Such an impression was unacceptable. The Panel was also concerned about the apparent lack of control exercised over the content of the invitations. High standards had not been maintained and a breach of Clause 9.1 was ruled.

Noting its rulings above and on balance, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

**Case AUTH/2565/11/12**

| | |
|---|---|
| **Complaint received** | **19 November 2012** |
| **Process commenced** | **4 December 2012** |
| **Case completed** | **22 March 2013** |

**Case AUTH/2566/11/12**

| | |
|---|---|
| **Complaint received** | **20 November 2012** |
| **Process commenced** | **4 December 2012** |
| **Case completed** | **22 March 2013** |

**Case AUTH/2567/11/12**

| | |
|---|---|
| **Complaint received** | **20 November 2012** |
| **Process commenced** | **4 December 2012** |
| **Case completed** | **15 March 2013** |

CASE AUTH/2568/12/12

# VOLUNTARY ADMISSION BY ASTELLAS

## Too many pages of advertising

**Astellas voluntarily admitted that the 5 December 2012 edition of Pulse included a one page Vesicare (solifenacin) advertisement plus a double-sided bound insert for the medicine. This was a potential breach of the Code.**

**The Authority's Constitution and Procedure required the Director to treat a voluntary admission as a complaint.**

**Astellas stated that its preliminary investigation suggested that it was not the fault of either Astellas or its agency which cancelled the additional advertisement in early November. Pulse had admitted full liability.**

**The detailed response from Astellas is given below.**

**The Panel noted that Astellas had initially booked a single page advertisement for the 5 December issue of Pulse but decided to replace it with a two page bound insert. Emails were clear about the revised instructions. Pulse confirmed the new instructions but mistakenly printed both the single page advertisement and the two page bound insert.**

**The Panel noted Astellas's submission that Pulse had admitted full responsibility for the error. However, it was an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf. The Panel considered that Astellas had been let down by its publisher.**

**The Panel noted that the 5 December issue of Pulse contained three pages of advertising for Vesicare, contrary to the requirements of the Code which limited advertising for a particular product to no more than two pages. A breach of the Code was ruled.**

Astellas Pharma Ltd made a voluntary admission in relation to Vesicare (solifenacin) advertisements published in Pulse 5 December 2012.

Paragraph 5.6 of the Authority's Constitution and Procedure stated that the Director should treat a voluntary admission as a complaint.

**COMPLAINT**

Astellas noted that in the 5 December edition of Pulse there were three pages of advertisements for Vesicare; a one page advertisement plus a double-sided bound insert. This was a potential breach of Clause 6.3.

Astellas stated that its preliminary investigation suggested that it was not the fault of either the company or its agency which cancelled the additional advertisement in early November. Astellas had an email from Pulse in which it admitted full liability and also the cancellation notification sent to Pulse from its agency dated 5 November.

When writing to Astellas, the Authority asked it to comment in relation to Clause 6.3 of the Code.

**RESPONSE**

Astellas stated that the initial arrangement was for a one page Vesicare advertisement (ref VES12419UK) to appear in the 5 December 2012 issue of Pulse. However, Astellas decided to withdraw this advertisement and replace it with a two page bound insert with both the original Vesicare (ref VES12419UK) advertisement alongside the VIP - Vesicare Information Programme (ref VES12431UK) patient support programme advertisement in order to highlight the availability of the free VIP service. Hence, the one page advertisement was dropped and the bound insert was chosen to limit the advertising of Vesicare, including VIP, to the permitted maximum of two pages as specified in Clause 6.3.

However, Astellas was informed by its agency on 5 December 2012 that Pulse carried the one page advertisement in error, in addition to the requested two page Vesicare and VIP bound insert. Astellas immediately investigated the reasons for this potential breach of Clause 6.3.

Astellas noted that on 6 November 2012 an email sent by the publisher of Pulse to Astellas's agency, confirmed the paperwork to remove the one page advertisement and replace it with the bound insert for the 5 December 2012 issue of Pulse. Unfortunately, although the publisher confirmed it would act on Astellas's agency's clear instructions, this did not happen and the 5 December issue of Pulse carried both the one page advertisement and the bound insert taking the total to three pages of Vesicare advertisements in spite of all the precautions taken by Astellas and the media buyer. The publisher subsequently admitted liability for this error and apologised in an email sent on 5 December 2012 and assured Astellas that this would not happen again.

Astellas submitted that it had very robust policies and procedures to ensure compliance with the Code. It had a standard operating procedure (SOP) for the withdrawal and recall of promotional and non-promotional materials but it did not have specific written guidance on the exchange of one advertisement slot for another. However, the communications between media buyer and publisher could not have been clearer and Astellas could not understand how this basic error had occurred. Astellas considered that it had been badly let down by the publisher.

In summary, Astellas submitted that the accidental publication of three pages of Vesicare advertisements occurred solely due to a mistake by Pulse and not an agency of Astellas and it therefore did not consider that it could be held accountable for a breach of Clause 6.3 as all reasonable steps were taken to prevent this.

Astellas hoped this clarified the situation and demonstrated that there was nothing more it could have done in this particular instance.

**PANEL RULING**

The Panel noted that Astellas had initially arranged for Pulse to publish a single page advertisement (ref VES12419UK) in the 5 December issue of the journal. It then decided to replace this advertisement with a two page bound insert consisting of the advertisement originally intended for publication alongside an advertisement for the Vesicare information programme. The Panel noted that emails were clear about the revised instructions; Pulse confirming that it had removed the one page advertisement and replaced it with the bound insert. The Panel further noted Astellas's submission that Pulse had then mistakenly printed both the single page and the two page bound advertisements.

The Panel noted Astellas's submission that Pulse had admitted full responsibility for the error. However, it was an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf. The Panel considered that Astellas had been let down by its publisher.

The Panel noted that the 5 December issue of Pulse contained three pages of advertisement for Vesicare, contrary to the requirements of Clause 6.3 which limited advertising for a particular product to no more than two pages. A breach of that clause was ruled.

**Complaint received** **12 December 2012**

**Case completed** **7 February 2013**

CASE AUTH/2569/12/12

# MERCK SHARP & DOHME v NOVO NORDISK

## Promotion of Victoza

Merck Sharp & Dohme complained about a Victoza (liraglutide) detail aid produced by Novo Nordisk.

The detail aid was headed 'The value of Victoza' and referred to the comparative effectiveness of oral antidiabetic medicines and glucagon-like peptide-1 (GLP-1) receptor agonists after metformin failure. Page 2 was headed 'Uncontrolled diabetes and its complications are a major health and economic burden'. Reference was made to the effects of a 1% reduction in $HbA_{1c}$, a 5% reduction in weight and reduced hypos (hypoglycaemic episodes). Page 3 referred to the failure of patients to reach their goals. This was followed by 'Victoza 1.2mg delivers benefits for patients with type 2 diabetes' followed by the claim 'With Victoza 1.2mg in combination with metformin, 32% of patients achieved the target of $HbA_{1c}$ <7%, weight loss or neutrality, and no hypoglycaemia' referenced to Zinman *et al* (2011). The page ended with three separate bullet points 'Reach their $HbA_{1c}$ target of <7%', 'Experience weight loss or no weight gain' and 'Experience no increase in the risk of hypoglycaemia'. Beneath these bullet points were three red boxes each linked with a plus sign which stated '$HbA_{1c}$<7%' 'weight loss or neutrality' and 'no hypos' respectively. Beneath the boxes was the statement 'Triple composite endpoint used in Zinman *et al*, 2011'. The red boxes appeared just above the Victoza brand logo which was the same shade of red.

Page 4 was headed 'More patients reach treatment targets with Victoza vs other treatments'. It compared a number of classes of oral antidiabetic medicines vs Victoza in relation to reaching the composite endpoint defined in Zinman *et al* which was described as 'Comparative effectiveness: Percentage of patients achieving HbA1c,< 7%, with no weight gain and no hypoglycaemic episodes'. The Victoza figure was 32%. The results for the other medicines shown were between 6% and 25%. The figure for DPP-IV inhibitor (Merck Sharp & Dohme's product sitagliptin (Januvia), 100mg daily) was 11%. The comparison was referenced to Zinman *et al*.

Page 5 was headed with the three coloured boxes showing the triple composite endpoint used on page 3. This was followed by the heading 'Fewer patients need to be treated with Victoza 1.2mg to get one patient to targets of $HbA_{1c}$ <7%, weight loss or neutrality, and no hypoglycaemia compared with other treatments'. The figures in the chart that followed was 3 people for Victoza; the figures for the other products were between 4 and 17. The claim was referenced to data on file (2011).

Page 6 was headed with the three coloured boxes showing the triple composite endpoint used on pages 3 and 5. This was followed by the heading 'Victoza 1.2mg is a cost-effective treatment for type 2 diabetes'.

Page 8 (the back cover) was headed 'Delivering more value than you might think' followed by 'Victoza helps patients with type 2 diabetes reach their treatment targets' and 'More patients reach $HbA_{1c}$ targets of <7% with weight loss or neutrality with Victoza 1.2mg than with all comparators, without increasing the rate of hypoglycaemia'. A number of claims followed finishing in a white box with '£To give patients an efficacious and cost-effective type 2 diabetes treatment post-metformin failure, consider starting them on Victoza today'. This was immediately followed by the red coloured boxes showing the triple composite endpoint used on pages 3, 5 and 6.

The detailed response from Novo Nordisk is given below.

Merck Sharp & Dohme was concerned about the substance and presentation of a post-hoc meta-analysis (Zinman *et al*), in which seven liraglutide trials were re-evaluated using a composite endpoint (achievement of $HbA_{1c}$ goal (defined as 7%), absence of hypoglycaemia and absence of weight gain) in an attempt to derive cost-effectiveness data for liraglutide vs the various comparators used in the studies.

Merck Sharp & Dohme was concerned that of the seven trials included in the analysis, (the LEAD (liraglutide effect and action in diabetes) -3 Mono trial, which contributed approximately 11% of the total analysis population) was a study of liraglutide monotherapy. As liraglutide was not licensed for monotherapy in the UK, inclusion of data was not in accordance with the Victoza marketing authorization. Furthermore, the use of such data could have biased the findings in favour of liraglutide as the efficacy of antidiabetic agents would be expected to be greater with earlier therapy; the reported incidence of hypoglycaemia increased with increasing duration of diabetes. None of the comparator agents in the analysis were evaluated as monotherapy.

The Panel noted that Zinman *et al* was a prespecified meta-analysis of 26 week patient level data from seven trials evaluating Victoza with commonly used treatments for type 2 diabetes adjusting for baseline $HbA_{1c}$ and weight, for a composite outcome of $HbA_{1c}$<7%, no weight gain and no hypoglycaemic events. The authors noted that although the differences in patient populations between the trials, in terms of previous antidiabetic therapy, were included as fixed effects in their analysis, there were limits to the conclusions that could be drawn from studies that differed in terms of background therapy.

The results showed that at 26 weeks, 40% of patients taking liraglutide 1.8mg and 32% of those taking 1.2mg achieved the composite outcome vs 6-25% of the comparators. As none of the studies used

**metformin as an active comparator Zinman *et al* was unable to objectively evaluate liraglutide vs metformin. The composite endpoint was chosen as it related to clinical issues of concern for both patient and physician. The authors stated that long-term outcome studies were required to determine if the improvement in the composite outcome reported would have significant long-term effects on clinical outcomes.**

**The Panel noted the patient numbers and that LEAD-3 Mono contributed more patients to the liraglutide 1.2mg group than any of the other studies. Liraglutide was not indicated as monotherapy. The Panel noted Merck Sharp & Dohme's comments about whether the monotherapy patient data was sufficiently similar to the combination data. Novo Nordisk provided data to show that LEAD-3 Mono did not appear to be an outlier with regard to decrease in $HbA_{1c}$ and that in the studies included in Zinman *et al* minor hypoglycaemia incidence did not consistently increase with increasing duration of diabetes.**

**The Panel noted that the detail aid did not refer to the use of Victoza as monotherapy. The licensed indication for Victoza as combination therapy was stated on the front page.**

**The Panel did not consider that reporting the results of Zinman *et al per se* promoted Victoza for an unlicensed indication or that the promotional material was inconsistent with the summary of product characteristics (SPC). Thus on the narrow grounds of the allegation it ruled no breach of the Code.**

**Merck Sharp & Dohme was concerned that the composite endpoint used in Zinman *et al* had been reproduced in prominent red boxes on several pages of the detail aid. This associated the substance of the composite endpoint with liraglutide itself, effectively representing a claim. One of the components of the endpoint was 'No hypoglycaemia', whereas hypoglycaemia was cited as a 'common' or 'very common' adverse effect in the Victoza SPC, Merck Sharp & Dohme thus alleged that this presentation was misleading.**

**The Panel examined the presentation of the composite endpoint in the detail aid. Each component was highlighted in a red box and the three boxes were joined with two plus signs. The same shade of red was used for some claims for Victoza and for the product logo. The Panel considered that the content, colouring and/or positioning of the red boxes would lead readers to conclude that all Victoza patients would have $HbA_{1c}$ <7%, lose weight or be weight neutral and have no hypos.**

**The Panel noted that the Victoza SPC stated that Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies (range 1-2.8kg). The SPC also stated that Victoza 1.2mg and glimepiride increased mean body weight by 0.32kg. The SPC listed hypoglycaemia as a common adverse reaction with Victoza and glimepiride and Victoza with metformin and rosiglitazone. It was listed as very common with Victoza with metformin and glimepiride.**

**The Panel considered that the presentation of the composite endpoint throughout the detail aid was, in effect, a claim for Victoza and misleading as alleged. The Panel did not consider that the footnote to the red boxes, 'Triple composite endpoint used in Zinman *et al*, 2011', negated the impression. A breach of the Code was ruled.**

**Merck Sharp & Dohme was also concerned about the comparison with Januvia. It believed that the use of a composite endpoint added nothing to the findings of the original study (Pratley *et al* 2010), given that there were no differences in the incidences of weight gain and hypoglycaemia between the liraglutide and sitagliptin study arms. Merck Sharp & Dohme alleged that the presentation of the liraglutide vs sitagliptin comparison was misleading, and possibly disparaging.**

**The Panel noted that pages 4 and 5 compared Victoza with a number of treatments, including Merck Sharp & Dohme's product sitagliptin. Pratley *et al* stated that mean weight loss after 26 weeks was significantly greater with Victoza than sitagliptin ($p < 0.0001$ for both doses of Victoza). The Panel noted the additional Novo Nordisk data on file whereby 20.8% of patients on Victoza 1.2mg plus metformin, 16.1% of patients on Victoza 1.8mg plus metformin and 37.4% of patients on sitagliptin plus metformin had increased body weight. The figures for decrease in body weight or no change were 79.2%, 84% and 62.6% respectively.**

**The Panel considered that there appeared to be a difference between the parties with regard to the weight data. The use of composite endpoints was not prohibited under the Code. Zinman *et al* showed the composite endpoint differences between Victoza 1.2mg and sitagliptin. It did not appear that this difference was only due to differences between the products in relation to attainment of $HbA_{1c}$<7% as alleged by Merck Sharp & Dohme. Whilst noting its rulings above, the Panel did not consider that the comparison with sitagliptin was misleading as alleged. Nor did the comparison disparage sitagliptin. No breaches of the Code were ruled.**

Merck Sharp & Dohme Limited complained about a Victoza (liraglutide) detail aid (ref UK/LR/0212/0048) produced by Novo Nordisk Limited. Novo Nordisk confirmed in inter-company dialogue that whilst the detail aid had been withdrawn from circulation, similar items remained in use. The complaint was thus referred to the Panel.

Victoza (for injection) was indicated for the treatment of adults with type 2 diabetes to achieve glycaemic control: in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea; in combination with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

The detail aid was headed 'The value of Victoza' and referred to the comparative effectiveness of oral antidiabetic medicines and glucagon-like peptide-1 (GLP-1) receptor agonists after metformin failure. Page 2 was headed 'Uncontrolled diabetes and its complications are a major health and economic burden'. It included a statement that effective treatment was associated with reduced complications and side effects. Reference was made to the effects of a 1% reduction in $HbA_{1c}$ a 5% reduction in weight and reduced hypos (hypoglycaemic episodes). Page 3 referred to the failure of patients to reach their goals. This was followed by 'Victoza 1.2mg delivers benefits for patients with type 2 diabetes' followed by the claim 'With Victoza 1.2mg in combination with metformin, 32% of patients achieved the target of $HbA_{1c}$ <7%, weight loss or neutrality, and no hypoglycaemia' referenced to Zinman *et al* (2011). The page ended with three separate bullet points 'Reach their $HbA_{1c}$ target of <7%', 'Experience weight loss or no weight gain' and 'Experience no increase in the risk of hypoglycaemia'. Beneath these bullet points were three red boxes each linked with a plus sign which stated '$HbA_{1c}$<7%' 'weight loss or neutrality' 'no hypos' respectively. Beneath the boxes was the statement 'Triple composite endpoint used in Zinman *et al*, 2011'. The red boxes appeared just above the Victoza brand logo which was the same shade of red.

Page 4 was headed 'More patients reach treatment targets with Victoza vs other treatments'. It compared a number of classes of oral antidiabetic medicines vs Victoza in relation to reaching the composite endpoint defined in Zinman *et al* which was described as 'Comparative effectiveness: Percentage of patients achieving $HbA_{1c}$,< 7%, with no weight gain and no hypoglycaemic episodes'. The Victoza figure was 32%. The results for the other medicines shown were between 6% and 25%. The figure for DPP-IV inhibitor (Merck Sharp & Dohme's product sitagliptin, 100mg daily) was 11%. The comparison was referenced to Zinman *et al*.

Page 5 was headed with the three coloured boxes showing the triple composite endpoint used on page 3. This was followed by the heading 'Fewer patients need to be treated with Victoza 1.2mg to get one patient to targets of $HbA_{1c}$ <7%, weight loss or neutrality, and no hypoglycaemia compared with other treatments'. The figures in the chart that followed was 3 people for Victoza; the figures for the other products were between 4 and 17. The claim was referenced to data on file (2011).

Page 6 was headed with the three coloured boxes showing the triple composite endpoint used on pages 3 and 5. This was followed by the heading 'Victoza 1.2mg is a cost-effective treatment for type 2 diabetes'.

Page 8 (the back cover) was headed 'Delivering more value than you might think' followed by 'Victoza helps patients with type 2 diabetes reach their treatment targets' and 'More patients reach $HbA_{1c}$ targets of <7% with weight loss or neutrality with Victoza 1.2mg than with all comparators, without increasing the rate of hypoglycaemia'. A number of claims followed finishing in a white box with '£To give patients an efficacious and cost-effective type 2 diabetes treatment post-metformin failure, consider starting them on Victoza today'. This was immediately followed by the red coloured boxes showing the triple composite endpoint used on pages 3, 5 and 6.

**1 Use of monotherapy data**

**COMPLAINT**

Merck Sharp & Dohme stated that its concerns, and the reasons underlying them, were set out in inter-company dialogue and summarized below.

Merck Sharp & Dohme was concerned about the substance and presentation of a post-hoc meta-analysis (Zinman *et al*), in which seven liraglutide trials were re-evaluated using a composite endpoint (achievement of $HbA_{1c}$ goal (defined as 7%), no hypoglycaemia and no weight gain) in an attempt to derive cost-effectiveness data for liraglutide vs the various comparators used in the studies.

Merck Sharp & Dohme was concerned that of the seven trials included in the analysis, one (the LEAD (liraglutide effect and action in diabetes) -3 Mono trial, which contributed approximately 11% of the total analysis population) was a study of liraglutide monotherapy vs glimepiride. Merck Sharp & Dohme alleged that as liraglutide was not licensed for monotherapy in the UK, inclusion of data from this trial was not in accordance with the marketing authorization for liraglutide in breach of Clause 3.2. Novo Nordisk had stated that the LEAD-3 data were included in an effort to be comprehensive and that monotherapy use was not specifically promoted in the detail aid. Nevertheless, Merck Sharp & Dohme did not believe that such considerations could exempt a company from its obligation under the Code not to use off-label data in its promotional materials.

Furthermore, the use of such data could have biased the findings in favour of liraglutide because the efficacy of any antidiabetic agent would be expected to be greater with earlier therapy; it was well accepted that the reported incidence of hypoglycaemia increased with increasing duration of diabetes. Both of these factors would have affected the comparative liraglutide results measured against the composite endpoint, particularly as (apart from glimepiride) none of the other comparator agents in the analysis were evaluated as monotherapy.

Merck Sharp & Dohme had suggested to Novo Nordisk that the Zinman *et al* analysis be re-calculated without the LEAD-3 data, but it had declined to do so.

**RESPONSE**

Novo Nordisk noted that the detail aid did not promote the use of liraglutide as a monotherapy treatment option for type 2 diabetes. The licensed indication for liraglutide was clearly stated on the front page.

Zinman *et al*, was a meta-analysis of all the available liraglutide phase 3 trials, including LEAD-3 Mono. The National Institute for Health and Clinical Excellence (NICE) Methods Guide for Technology Appraisal defined meta-analysis as a statistical technique for combining (pooling) the results of a number of studies that addressed the same question and reported on the same outcomes to produce a more precise summary estimate of the effect on a particular outcome.

The Zinman *et al* data was used in the detail aid to show a comparison of liraglutide 1.2mg in reaching the clinically important outcome of achieving a target $HbA_{1c}$ without weight gain or hypoglycaemia vs other available treatment options including glimepiride, rosiglitazone, sitagliptin, exenatide and glargine. When the meta-analysis was conducted there were seven phase 3 trials available which included 4,625 patients. Without the meta-analysis, liraglutide could not be collectively compared to all the aforementioned treatments; instead it could only be compared to individual medicines. Novo Nordisk noted that LEAD-3 Mono contributed just 10.7% (498) of the overall number of patients in the analysis.

In relation to hypoglycaemia, Novo Nordisk provided a table summarising the data from the studies used in Zinman *et al* which had been generated by referring to the individual published studies but also data on file from the Integrated Clinical Trial Report. With an increase in the duration of diabetes there was no consistent decrease in liraglutide efficacy (measured as $HbA_{1c}$ decrease or as the percentage of patients reaching <7% $HbA_{1c}$, as in Zinman *et al*) or increase in reported hypoglycaemia when LEAD-3 was compared with the other studies. When referring to the summary of liraglutide trial data, Novo Nordisk noted that the data on efficacy for LEAD-3 did not appear to be an outlier. Furthermore, the rates of hypoglycaemia were higher in LEAD-3 compared with most of the other studies, with the exception of LEAD-5 and LEAD-6 where liraglutide was used concomitantly with a sulphonylurea.

Taking the above into account, it was likely that by excluding LEAD-3 data, the outcome of Zinman *et al* would have favoured liraglutide even more. Novo Nordisk reiterated that by including all relevant studies in Zinman *et al*, it wanted to be as comprehensive as possible and not be accused of selectively using the data.

Meta-analysis was commonly used in NICE technology appraisals. The Methods Guide for Technology Appraisal outlined the following: 'Synthesis of outcome data through meta-analysis is appropriate provided there are sufficient relevant and valid data that use measures of outcome that are comparable'.

As more new diabetes treatments became available there would be an increasing demand to compare these with the efficacy of existing therapies. It would never be possible to perform comparative trials against all existing therapies and therefore these analyses would increasingly rely on network meta-analyses to guide payers and health professionals.

Network meta-analysis built on the principles of meta-analysis and created an analysis that compared two or more interventions using a combination of direct evidence (from head-to-head trials of the interventions of interest) and indirect evidence (trials that did not compare the interventions of interest directly in head-to-head trials).

The NICE Methods Guide stated that the principles of good practice for standard meta-analyses should also be followed in mixed and indirect treatment comparisons. Furthermore, ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Taskforce recommendations on conducting indirect-treatment-comparison and network meta-analysis studies stated that unlicensed treatments in some instances might contribute to the evidence network.

Network meta-analysis in diabetes was complex due to the number of available treatment options and the complexity of the treatment pathway. If such analysis could only include evidence for licensed indications, this would add greater complexity to what would already be a complex meta-analyses if the statisticians had to assess whether all of the identified studies complied fully with the licensed indication. This would pose even greater problems where studies might report the results of trials where the licensed vs unlicensed population was combined and patient level data was not available. Furthermore, if it was ruled that meta-analysis and network meta-analysis used for promotional purposes should only be based on evidence from licensed indications, this might create different efficacy and safety values to those in peer reviewed publications and/or health technology submissions. This could create confusion and question the credibility of such analyses thereby creating a controversial issue not only for Novo Nordisk but for all of the companies going forward.

Based on the above, Novo Nordisk did not believe that it had promoted liraglutide outside of the marketing authorization and denied a breach of Clause 3.2.

**PANEL RULING**

The Panel noted that Zinman *et al* was a prespecified meta-analysis of 26 week patient level data from seven trials evaluating Victoza with commonly used treatments for type 2 diabetes adjusting for baseline $HbA_{1c}$ and weight, for a composite outcome of $HbA_{1c}$<7%, no weight gain and no hypoglycaemic events. The authors noted that although the differences in patient populations between the trials, in terms of previous exposure to antidiabetic therapy, were included as fixed effects in their analysis, there were limitations to the conclusions that could be drawn from studies that differed in terms of background therapy.

The results showed that at 26 weeks, 40% of patients taking liraglutide 1.8mg and 32% of those taking 1.2mg achieved the composite outcome vs 6-25% of the comparators. As none of the studies used metformin as an active comparator Zinman *et al* was

unable to objectively evaluate the performance of liraglutide vs metformin with this composite outcome approach. The authors chose the composite endpoint as it specifically related to clinical issues of concern for both patient and physician. The authors stated that long-term outcome studies were required to determine if the improvement in the composite outcome reported would have significant long-term effects on clinical outcomes.

The Panel noted that the detail aid promoted Victoza 1.2mg. Zinman *et al* evaluated the results of 4,625 patients of which 1,581 were on Victoza 1.8mg and 1,117 were on Victoza 1.2mg. LEAD-3 Mono studied 251 patients taking Victoza 1.2mg and 247 patients taking Victoza 1.8mg. Thus LEAD-3 Mono was carried out on 251/1,117 ie 22.5% of Victoza 1.2mg patients. LEAD-3 Mono contributed more patients to the liraglutide 1.2mg group than any of the other studies. Liraglutide was not indicated as monotherapy. The Panel noted Merck Sharp & Dohme's comments about whether the monotherapy patient data was sufficiently similar to the combination data given that monotherapy was used earlier in the treatment pathway and the efficacy of any antidiabetic therapy would be expected to be greater with earlier therapy and that the reported incidence of hypoglycaemia increased with increasing duration of diabetes. Novo Nordisk provided data to show that LEAD-3 Mono did not appear to be an outlier with regard to decrease in $HbA_{1c}$ and that in the studies included in Zinman *et al* minor hypoglycaemia incidence did not consistently increase with increasing duration of diabetes.

The Panel noted that the detail aid did not refer to the use of Victoza as monotherapy. The licensed indication for Victoza as combination therapy was stated on the front page.

The Panel noted that Zinman *et al* was incorrectly referenced in the list of references as Zinman *et al* (2012). Zinman *et al* included a study (LEAD-3, Mono), that investigated Victoza as monotherapy. The Panel did not consider, however, that reporting the results of Zinman *et al per se* promoted Victoza for an unlicensed indication or that the promotional material was inconsistent with the summary of product characteristics (SPC). Thus on the narrow grounds of the allegation it ruled no breach of Clause 3.2.

**2 Composite endpoint claims**

**COMPLAINT**

Merck Sharp & Dohme was concerned that the composite endpoint used in Zinman *et al* had been reproduced in prominent red boxes on several pages of the detail aid. There was no reason for this highly unusual practice other than to associate, in the reader's mind, the substance of the composite endpoint with liraglutide itself, effectively representing a claim. Given that one of the components of the composite endpoint was 'No hypoglycaemia', whereas hypoglycaemia was cited as a 'common' or 'very common' adverse effect in the Victoza SPC, Merck Sharp & Dohme alleged that this presentation was potentially highly misleading in breach of Clause 7.2. Merck Sharpe & Dohme did not consider that Novo Nordisk's offer to embolden the clarifying statement that appeared under each occurrence, would significantly mitigate the clear overall impression given by the manner in which the composite endpoint was used in the detail aid.

**COMPLAINT**

Merck Sharp & Dohme was concerned that the composite endpoint used in Zinman *et al* had been reproduced in prominent red boxes on several pages of the detail aid. There was no reason for this highly unusual practice other than to associate, in the reader's mind, the substance of the composite endpoint with liraglutide itself, effectively representing a claim. Given that one of the components of the composite endpoint was 'No hypoglycaemia', whereas hypoglycaemia was cited as a 'common' or 'very common' adverse effect in the Victoza SPC, Merck Sharp & Dohme alleged that this presentation was potentially highly misleading in breach of Clause 7.2. Merck Sharpe & Dohme did not consider that Novo Nordisk's offer to embolden the clarifying statement that appeared under each occurrence, would significantly mitigate the clear overall impression given by the manner in which the composite endpoint was used in the detail aid.

**RESPONSE**

Novo Nordisk stated that the composite endpoint within the red box was displayed at relevant points in the detail aid to remind the user of the composite endpoint of Zinman *et al*. Merck Sharp & Dohme claimed that this misled the reader into associating the endpoints with liraglutide itself. Feedback from health professionals had highlighted that the notion of a composite endpoint was not easily understood, so this provided an apt reminder of the three outcomes combined in the endpoint. The red box was only used at the points where the composite endpoint data was shown and was clearly referenced to Zinman *et al*. Novo Nordisk disagreed that detailing the composite endpoint in this way was in breach of Clause 7.2.

**PANEL RULING**

The Panel examined the presentation of the composite endpoint in the detail aid. Each component of the endpoint was highlighted in a red box and the three boxes were joined with two plus signs. The same shade of red was used for some claims for Victoza and for the product logo. The Panel considered that the content, colouring and/or positioning of the red boxes would lead readers to conclude that all Victoza patients would have $HbA_{1c}$ <7%, lose weight or be weight neutral and have no hypos. In this regard the Panel noted that on page 3 in particular, the red boxes describing the composite endpoint '$HbA_{1c}$<7% + weight loss or neutrality + no hypos' appeared immediately after the claim 'Victoza 1.2mg delivers benefits for patients with type 2 diabetes' and just above the product logo. Given the positioning and use of colour, the reader would link all three together. The back page of the detail aid was

headed, in red, 'Delivering more value than you might think'. The three red boxes appeared on the lower half of the page and the red product logo was in the bottom right hand corner. Again the Panel considered that the reader's eye would be drawn to all three and '$HbA_{1c}$ <7% + weight loss or neutrality + no hypos' would be seen as a claim for Victoza ie delivering more than the reader might think. Whilst Zinman *et al* had shown that some patients on Victoza 1.2mg would achieve the composite endpoint, it was only in a minority ie 32%.

The Panel noted that the Victoza SPC stated that Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies (range 1-2.8kg). The SPC also stated that Victoza 1.2mg and glimepiride increased mean body weight by 0.32kg. The SPC listed hypoglycaemia as a common adverse reaction with Victoza and glimepiride and Victoza with metformin and rosiglitazone. It was listed as very common with Victoza with metformin and glimepiride.

The Panel considered that the presentation of the composite endpoint throughout the detail aid was, in effect, a claim for Victoza and misleading as alleged. The Panel did not consider that the footnote to the red boxes, 'Triple composite endpoint used in Zinman *et al*, 2011', negated the impression. A breach of Clause 7.2 was ruled.

**3 Comparison with sitagliptin**

**COMPLAINT**

Merck Sharp & Dohme was also concerned about the comparison with its product sitagliptin (Januvia). It believed that the use of a composite endpoint added nothing to the findings of the original study (Pratley *et al* 2010), given that there were no differences in the incidences of weight gain and hypoglycaemia between the liraglutide and sitagliptin study arms. Its position was set out in detail in inter-company dialogue. Novo Nordisk had declined to make it clear that there were no differences between the two medicines in these parameters. Merck Sharp & Dohme alleged that the presentation of the liraglutide vs sitagliptin comparison was misleading, and possibly disparaging, in breach of Clauses 7.2 and 8.1.

**RESPONSE**

Novo Nordisk submitted that in Pratley *et al*, liraglutide significantly decreased body weight compared with sitagliptin. In addition, data from the ICTR (Integrated Clinical Trial Report) for Pratley *et al* showed that 37.4% of patients gained weight in the sitagliptin arm compared with 20.8% and 16.1% in the liraglutide 1.2mg and 1.8mg arms respectively. This clearly demonstrated that liraglutide was superior compared with sitagliptin in two items of the composite endpoint (percentage of patients reaching target of $HbA_{1c}$ <7% and number of patients without weight gain). As the results relating to weight gain had not been published previously, including this as part of Zinman *et al* added to the body of evidence to demonstrate the efficacy and safety of liraglutide vs other available treatments. Novo Nordisk did not consider that the presentation of the liraglutide vs sitagliptin data in the detail aid was either misleading or disparaging. Novo Nordisk therefore denied a breach of Clauses 7.2 and 8.1.

**PANEL RULING**

The Panel noted that pages 4 and 5 compared Victoza with a number of treatments, including Merck Sharp & Dohme's product sitagliptin. Pratley *et al* stated that mean weight loss after 26 weeks was significantly greater with Victoza than sitagliptin ($p < 0.0001$ for both doses of Victoza). The Panel noted the additional Novo Nordisk data on file whereby 20.8% of patients on Victoza 1.2mg plus metformin, 16.1% of patients on Victoza 1.8mg plus metformin and 37.4% of patients on sitagliptin plus metformin had increased body weight. The figures for decrease in body weight or no change were 79.2%, 84% and 62.6% respectively.

The Panel considered that there appeared to be a difference between the parties with regard to the weight data. The use of composite endpoints was not prohibited under the Code. Zinman *et al* showed the composite endpoint differences between Victoza 1.2mg and sitagliptin. It did not appear that this difference was only due to differences between the products in relation to attainment of $HbA_{1c}$<7% as alleged by Merck Sharp & Dohme. Whilst noting its ruling in Point 2 above, the Panel did not consider that the comparison with sitagliptin was misleading as alleged. No breach of Clause 7.2 was ruled. Nor did the comparison disparage sitagliptin and no breach of Clause 8.1 was ruled.

**Complaint received** **17 December 2012**

**Case completed** **25 February 2013**

# ANONYMOUS HEALTH PROFESSIONAL v PHARMACOSMOS

## Symposium invitation

**An anonymous, non-contactable complainant who described themselves as a health professional complained about an invitation to a Pharmacosmos symposium at a European congress to take place in Vienna, February 2013. The invitation asked 'Can we optimize treatment with single high dose intravenous iron in IBD [inflammatory bowel disease] patients? – *New data from clinical trials'.* Pharmacosmos marketed Monofer (iron as iron (III) isomaltoside 100) and CosmoFer (iron dextran)). Both products were for the intravenous treatment of iron deficiency and both could be administered as total dose infusions.**

**The complainant stated that the material was supposed to be new and therefore he/she did not understand how it could be discussed or promoted until published and licensed.**

**The detailed response from Pharmacosmos is given below.**

**The Panel noted that the front page of the flyer featured a headline banner which read 'Invitation'. The reader was then invited to save the date for the Pharmacosmos symposium followed by the statement 'Can we optimize treatment with single high dose intravenous iron in IBD patients? - *New data from clinical trials.*' The background picture was of someone adjusting the flow of an intravenous drip. The reverse featured similar details about the date, time and location of the symposium above corporate information about Pharmacosmos and referred to treatment options with maximum efficacy, convenience and safety for patients and professionals. Readers were invited to visit the corporate website for more information.**

**Although the Panel noted that it was confined to considering the content of the flyer it further noted that discussion or promotion of medicines based on unpublished clinical data was not universally prohibited as implied by the complainant. The use of data, be it published or otherwise, to promote an unlicensed product or indication was prohibited by the Code, however the legitimate exchange of medical and scientific information was allowed in limited circumstances.**

**The Panel noted that as submitted by Pharmacosmos the new data from clinical trials to be discussed at the symposium was about Monofer, however that was not stated or implied anywhere on the flyer. The flyer referred to single high dose intravenous iron in IBD patients. The Panel noted that Monofer and, in limited circumstances CosmoFer, could be administered as a single total dose infusion. The Panel considered that the flyer did not directly or indirectly refer to either medicine and thus was not promotional as implied by the complainant. The requirement to include prescribing information did not apply and no breach of the Code was ruled. As a consequence of its finding that the flyer was not promotional the Panel made other rulings of no breach of the Code.**

An anonymous, non-contactable complainant who described themselves as a health professional complained about a double sided, A5 invitation to a Pharmacosmos symposium at the 8th Congress of ECCO (European Crohn's and Colitis Organisation) to take place in 14-16 February 2013. The invitation asked 'Can we optimize treatment with single high dose intravenous iron in IBD [inflammatory bowel disease] patients? – *New data from clinical trials*'. Pharmacosmos marketed Monofer (iron as iron (III) isomaltoside 100) and CosmoFer (iron dextran)). Both products were for the intravenous treatment of iron deficiency and both could be administered as total dose infusions.

**COMPLAINT**

The complainant stated that he/she had just transferred to a London hospital and the invitation was in the department. However, the material was supposed to be new and therefore the complainant did not understand how it could be discussed or promoted until published and licensed.

When writing to Pharmacosmos A/S, the Authority asked it to respond in relation to Clauses 3.1, 3.2, 4.1, 9.1 and 2 of the Code.

**RESPONSE**

Pharmacosmos stated that as the complaint was both anonymous and general, it was difficult to investigate any specific aspect of the matter. The complaint did not specify which aspect of the invitation gave cause for concern, other than that the data might not be within the product licence. Since the invitation did not identify a specific product in any capacity, it was not practical for the reader to identify a product licence against which the comments should be made.

Pharmacosmos submitted that twenty of the approved symposium flyers were given to each of its UK representatives in early October following its UK sales conference. Pharmacosmos would attend the ECCO conference. The Pharmacosmos symposium was open to all conference attendees it was an official part of the agenda and as such was a legitimate occasion for scientific exchange regarding treatments and products. Information about the symposium and all industry symposia was available from the conference organizer's website. Pharmacosmos noted that Clauses 3.1 and 3.2 related to promotional activity (or activity that was deemed to be promotional).

The purpose of the flyer was to inform physicians attending the conference that Pharmacosmos would hold a scientific symposium at the conference. There was no intention to distribute the flyer more widely and so Pharmacosmos had not regarded this as a promotional piece *per se*. There was no reference on the flyer to a *specific* product and no mention of any product name. While Pharmacosmos recognised these were not the only determinants of promotion, these were key considerations when reviewing this item in combination with the intention that it would only be given to health professionals known to be attending ECCO. Indeed, there would be little value in providing the flyer to those who would not attend ECCO because the symposium was part of the main conference and could not be attended by any physician who was not registered for the conference. It was unclear how the flyer ended up on a hospital department noticeboard; Pharmacosmos assumed it was placed there by a well-meaning colleague of the complainant.

Pharmacosmos submitted that there was nothing in the title of the symposium, 'Can we optimise treatment with single high dose intravenous iron in IBD patients? – *New data from clinical trials*', which would indicate use of any particular product. Pharmacosmos noted that Monofer was already licensed for high dose intravenous use in IBD and that the presentation was intended to be about Monofer data. However, Monofer and its licence status were not directly identifiable from the flyer.

Pharmacosmos submitted that as the complaint had been received six weeks before the symposium was due to be held the presentations were not written and thus had not been submitted to Pharmacosmos for review. However, a copy of the symposium agenda was provided. Neither the agenda nor any other material about the symposium had been given to any UK health professionals.

Given all the circumstances, Pharmacosmos denied breaches of Clauses 3.1 and 3.2.

Pharmacosmos and other companies made a number of products related to intravenous iron therapy, the majority of which were suitable for use in patients with IBD. On that basis Pharmacosmos stated that the invitation did not identify any specific product. Pharmacosmos would not normally add obligatory information to meetings invitations unless the invitation text specifically named or indicated a specific product. An Appeal Board ruling had made it clear that a reference to a class of treatment was not promotional *per se* unless a specific treatment was identifiable (Case AUTH/2482/2/12).

Given that the material did not promote a specific medicine, there was no requirement for prescribing information to be included. Pharmacosmos thus denied a breach of Clause 4.1.

Pharmacosmos was grateful that the concerns had been raised and for the opportunity to comment; further it denied breaching Clauses 2, and 9.1 of the Code.

**PANEL RULING**

The Panel noted that the front page of the 2 page flyer featured a headline banner which read 'Invitation'. The reader was then invited to save the date for the Pharmacosmos symposium followed by the statement 'Can we optimize treatment with single high dose intravenous iron in IBD patients? - *New data from clinical trials.*' The background picture was of someone adjusting the flow of an intravenous drip. The reverse featured similar details about the date, time and location of the symposium above corporate information about Pharmacosmos and referred to treatment options with maximum efficacy, convenience and safety for patients and professionals. Readers were invited to visit the corporate website for more information.

The complainant's concern was that new material could not be discussed or promoted until it was published or licensed and in this regard the Panel noted that it was confined to considering the content of the flyer. The Panel noted that discussion or promotion of medicines based on unpublished clinical data was not universally prohibited as implied by the complainant. The use of data, be it published or otherwise, to promote an unlicensed product or indication was prohibited by Clauses 3.1 and 3.2, however the discussion of such data might be permitted in those limited circumstances set out in the supplementary information to Clause 3, Marketing Authorisation, regarding the legitimate exchange of medical and scientific information.

The Panel queried whether the flyer had been distributed solely to physicians attending the conference as submitted by Pharmacosmos. The target audience on the relevant job bag form was described simply as 'gastro clinicians' and each UK representatives had been provided with twenty although the Panel did not know how they were briefed to use them and how many had been distributed.

The Panel firstly had to decide whether the flyer was promotional. The Panel noted that as submitted by Pharmacosmos the new data from clinical trials to be discussed at the symposium was about Monofer, however that was not stated or implied anywhere on the flyer. The flyer referred to single high dose intravenous iron in IBD patients. The Panel noted that, in limited circumstances, both Monofer and CosmoFer could be administered as a single total dose infusion. The Panel considered that the flyer did not directly or indirectly refer to either medicine and was thus not promotional Monofer as implied by the complainant. The requirement to include prescribing information did not apply and thus no breach of Clause 4.1 was ruled. Noting its finding that the flyer was not promotional the Panel also ruled no breach of Clauses 3.1 and 3.2. The Panel consequently ruled no breach of Clauses 2 and 9.1.

**Complaint received** **20 December 2012**

**Case completed** **6 February 2013**

**CASE AUTH/2577/2/13**

# VOLUNTARY ADMISSION BY ABBVIE

## Out-of-date prescribing information

**Abbvie voluntarily admitted that out-of-date prescribing information had been linked to an online Humira (adalimumab) banner advertisement and included in a hard copy Humira journal advertisement. The materials at issue, which were published in December 2012, promoted Humira for the treatment of moderate to severe, active rheumatoid arthritis.**

**The detailed response from Abbvie is given below.**

**The Panel noted that as the banner advertisement had appeared on a UK website and the journal advertisement had been published in international journals which were based in the UK, they both came within the scope of the Code. Although the material had been placed by Abbvie's global group, it was a well established principle under the Code that UK companies were responsible for the acts or omissions of overseas parents or affiliates that came within the scope of the Code.**

**The Code stated that the prescribing information consisted of, *inter alia*, a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications relevant to the indications in the advertisement. The Panel noted that the prescribing information at issue was last revised in May 2011 and did not include two common side-effects and two serious, uncommon side-effects of Humira that were included in the December 2012 prescribing information. The Panel considered that as the prescribing information linked to the banner advertisement and included in the journal advertisements was not up-to-date with regard to precautions and side-effects it did not comply with the Code. High standards had not been maintained. Breaches of the Code were ruled.**

Abbvie Ltd voluntarily admitted that out-of-date prescribing information had been linked to an online Humira (adalimumab) advertisement (ref AXHUR111644a) and included in a hard copy Humira advertisement (ref AXHUR111644) which was published in four journals. The material at issue promoted Humira for the treatment of moderate to severe, active rheumatoid arthritis.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Abbvie.

**COMPLAINT**

Abbvie submitted that it had become aware of a potential breach of the Code and drew attention to an online banner advertisement for Humira placed on rheumatology.org.uk on 17 December 2012 by the global rheumatology team. The advertisement had been approved by the UK affiliate in October 2011. On inspection it became clear that the linked prescribing information was now out-of-date (ie version 23) contrary to Clause 4.2 of the Code.

Abbvie contacted the publisher and requested the immediate removal of the banner advertisement. The advertisement was taken down within an hour of Abbvie knowing about the breach. Abbvie also contact the advertising agencies involved and its global colleagues. Both confirmed that there was no other online advertising using the same out-of-date prescribing information.

In the course of these communications, Abbvie also became aware that on 17 December 2012 the global rheumatology team had commissioned the printed advertisements. These advertisements had also been approved by the UK affiliate in October 2011, but also now included prescribing information which was out-of-date (version 23). The advertisements were scheduled to appear in Annals of Rheumatic Disease, Rheumatology, International Rheumatology and Clinical Rheumatology. The first two of these journals were based in the UK.

On becoming aware of this, Abbvie requested the print run to be stopped but was unfortunately too late to stop the out-of-date advertisements appearing in the January 2013 editions of the journals, in breach of Clause 4.2. The advertisement had been withdrawn from all future issues.

In summary, Abbvie submitted that it became aware of two incidents where outdated prescribing information was included in an online advertisement and printed journal advertisements for Humira. The online advertisement was withdrawn as a matter of urgency and the printed advertisements had been withdrawn from future issues.

After an investigation, including a review of processes involved, Abbvie believed that this was an isolated incident. The incident was an individual's error, rather than Abbvie processes which were not followed by a new employee. Retraining of the employee was underway.

In terms of further preventative measures, an updated global standard operating procedure (SOP) was in development. This would mandate that global marketing could not make promotional advertisements on behalf of an affiliate, and only an affiliate could make a placement in its local market.

Abbvie considered that there was no risk to patient safety arising from this incident and the correct prescribing would have been available through

many other sources. Abbvie took its obligations to transparency under the Code very seriously and so wanted to bring this matter to the Authority's attention.

When writing to Abbvie, the Authority asked it to respond to Clauses 4.2 and 9.1 of the Code.

**RESPONSE**

Abbvie submitted that global colleagues requested UK approval of advertisements which were to be run in rheumatology journals and online in October 2011. Electronic copies were provided which included the then Humira prescribing information (version 23). Abbvie noted that the advertisements were used again on 17 December 2012. These advertisements had been commissioned by Abbvie global, without further approval from the UK. The correct Humira prescribing information in December 2012 was version 27. The advertisements were placed on rheumatology.org.uk and printed in Annals of Rheumatic Disease, Rheumatology, International Rheumatology and Clinical Rheumatology.

The online banner advertisement was withdrawn immediately but the journal advertisement had already gone to print and appeared in the January 2013 editions of the journals listed above. Printed advertisements had been withdrawn from all future issues.

Annals of Rheumatic Disease and Rheumatology were both published in the UK. The Humira advertisement at issue would only be seen by subscribers in the UK and Europe. As previously stated, Abbvie believed these journals would be subject to the Code. Clinical Rheumatology and Rheumatology International were international journals published in Germany. Abbvie did not consider that these journals were subject to the Code.

By chance, an Abbvie UK employee noted that the date of preparation of the online banner advertisement was October 2011 and checked the prescribing information; the matter was then escalated to the medical department.

Abbvie provided internal policy documents current when the advertisements were published and also provided details of the dates when the Humira prescribing information had been updated from version 23 (included on the material at issue) to the current version (version 27, revised December 2012). Abbvie submitted that the prescribing information was extensively rewritten and simplified in December 2012 so a direct comparison of version 27 with version 23 was not possible.

The major changes between versions 23 and 27 were:

- Version 23 did not contain the ulcerative colitis, paediatric Crohn's or nonradiographic-axial spondyloarthropathy indications.
- Version 23 did not refer to the following adverse events: nerve root compression, pyrexia (both common), specific wording regarding Merkel cell carcinoma and liver failure (both serious uncommon). Previous versions of the prescribing information included general statements regarding increased risk of malignancy.
- Under Precautions, the time relating to monitoring patients for infections has reduced from 5 months to 4 months in version 27.

When prescribing information was updated, regulatory affairs emailed the marketing department which then had to update materials or withdraw and notify all parties and ensure the return of any outstanding hard copy material for destruction. Unfortunately, due to an individual error in this case, a new employee did not follow this process. The employee had been trained on the policy in September 2011 and Abbvie had not identified any other examples where the individual in question had made the same error. Action regarding retraining the employee was underway. The promotional materials in question were withdrawn in October 2012.

Abbvie considered that this was an isolated incident and reflected an individual's error rather than Abbvie processes which were not followed by a new employee.

**PANEL RULING**

The Panel noted that the banner advertisement at issue had appeared on a UK website (rheumatology.org.uk) and the hard copy advertisement at issue had been published in international journals which were based in the UK (Annals of Rheumatic Disease and Rheumatology). The Panel thus considered that the materials came within the scope of the Code. Although the material had been placed by Abbvie's global group, it was a well established principle under the Code that UK companies were responsible for the acts or omissions of overseas parents or affiliates that came within the scope of the Code.

The Panel noted that Clause 4.1 of the Code required the prescribing information listed in Clause 4.2 to be provided in a clear and legible manner. Clause 4.2 stated the prescribing information consisted of, *inter alia*, a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications relevant to the indications in the advertisement. The Panel noted that the prescribing information included on the online advertisement and in the journal advertisements was last revised in May 2011 and did not include the common side-effects of nerve root compression and pyrexia; nor were the serious, uncommon side-effects of Merkel cell carcinoma and liver failure included. Under precautions the prescribing information on the online advertisement and in the journal advertisements stated that because of the susceptibility of Humira patients to serious infections compounded by possible impaired lung function, patients should be closely monitored for infections, including tuberculosis, before, during and for 5 months after treatment with Humira. The prescribing information had been changed such that the

monitoring period had been reduced to 4 months. The Panel further noted that although the prescribing information at issue did not refer to three particular indications, it did refer to rheumatoid arthritis which was the subject of the advertisements at issue. Clause 4.2 also stated that at least one authorized indication for use had to be given and this had been done. However, the Panel considered that as the prescribing information linked to the banner advertisement and included in the journal advertisements was not up-to-date with regard to precautions and side-effects it did not comply with the Code. As Clause 4.1 required that the prescribing information be provided a breach of that clause was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. Up-to-date prescribing information had not been provided. A breach of Clause 9.1 was ruled.

**Complaint received** **6 February 2013**

**Case completed** **14 March 2013**

# JOURNALIST v NOVARTIS

## Daily Mail article

**A journalist alleged that an article entitled 'Don't scrap asthma jab that saved my son's life', published in the Daily Mail online, promoted Xolair (omalizumab), marketed by Novartis. The complainant noted that no-one from Novartis was mentioned in the article but that others who were quoted were connected to the company. The complainant assumed that Novartis had had a hand in the article which was a one-sided account of Xolair.**

**The detailed response from Novartis is given below.**

**The Panel noted that when complaints were received about what an independent journalist had published in the press, its rulings were made upon the material released by the company that might have prompted the article, not the article itself.**

**The Panel noted the time delay between the relevant press release being issued (9, November 2012) and the publication of the article at issue (11, February 2013). Although the press release was about a draft decision by the National Institute for health and Clinical Excellence (NICE) to revoke existing positive guidance on the use of Xolair in patients aged 12 and above, it did not otherwise appear to have influenced the content of the article in the Daily Mail. The article was principally one mother's story about her 14 year old son and concluded with a general discussion about the potential negative impact of the draft NICE recommendation on patient care. The article quoted a spokesperson from Asthma UK, a hospital consultant in respiratory medicine and included a pack shot of Xolair which Novartis submitted was not a UK pack. The Panel noted that the press release did not refer to the 14 year old boy and although it quoted two hospital physicians, neither were the consultant quoted in the article. The press release did not refer to Asthma UK. The Panel noted Novartis's submission that neither it nor its PR agency had engaged with the author over the story nor did it know about the case study presented.**

**The Panel noted that the article was quite different to the press release; the press release had been issued three months before the article was published. The Panel noted the content of the press release and did not consider that it promoted Xolair to the public. No breach of the Code was ruled.**

**The Panel noted that the article described Xolair in very positive terms but that the tone of the press release was quite different and did not appear to have led to the strong, unequivocal claims in the article. The Panel thus ruled no breach of the Code.**

**The Panel considered that high standards had been maintained. No breach of the Code was ruled including no breach of Clause 2.**

A journalist alleged that an article entitled 'Don't scrap asthma jab that saved my son's life' and published 11 February 2013 in the Daily Mail online, promoted Xolair (omalizumab), marketed by Novartis Pharmaceuticals UK Ltd. Xolair was indicated only for the treatment of patients with convincing IgE (immunoglobulin E) mediated asthma.

The relevant press release issued by Novartis was entitled 'NICE [National Institute for health and Clinical Excellence] draft decision on omalizumab (Xolair) could leave people with the most severe form of asthma without an effective and innovative treatment option' and detailed a draft decision by NICE not to recommend the use of Xolair for the treatment of severe persistent allergic asthma which revoked existing positive guidance. The efficacy of Xolair vs alternative treatment options was discussed as was the burden of severe asthma. The press release included quotations from senior health professionals.

**COMPLAINT**

The complainant alleged that the Daily Mail article was thinly veiled promotion for Xolair. No-one from Novartis was explicitly mentioned in the article but a quick Google search found that a consultant in respiratory medicine who the paper spoke to, had attended advisory boards for, *inter alia*, Novartis as he declared in a recent BMJ article. The complainant also noted that Asthma UK, who's chief executive was interviewed in the piece, was also funded by Novartis to the tune of around £45,000 in 2011.

The complainant submitted that the article stated that other medicines were bad and Xolair was better and implied heavily that NICE should not reject its use on the NHS – all points Novartis emphatically agreed with – and this was not surprising given that two of those interviewed for the article had direct relations with the company.

The complainant assumed that Novartis had had a hand in the story being made known to Asthma UK and the Daily Mail, and the story was very one-sided in its blatant promotion of a prescription only medicine – the article also included a pack shot of Xolair, which the complainant knew from experience could only be obtained from a pharmaceutical company as it needed to be signed off for use.

The complainant stated that Novartis had probably done enough to escape censure under the Code, but he asked that the Authority investigate whether this was so. The complainant also asked that this type of behaviour be reviewed when the Code was next updated, as it made a mockery of policing pharmaceutical companies when they could find way to promote medicines on the world's biggest online news site.

When writing to Novartis, the Authority asked it to consider the requirements of Clauses 2, 9.1, 22.1 and 22.2 of the Code.

**RESPONSE**

Novartis submitted that it was not involved in the generation of the article.

Novartis stated that it issued a press release in November 2012 (copy provided) shortly after the draft decision from NICE to revoke its current positive guidance for Xolair use in patients aged 12 years and older.

Novartis also confirmed that neither it nor its PR agency had engaged with the author of the article at any point over this story. Nor did it have any interaction or knowledge of the case studies used in the article.

Novartis had, in line with the Code, complied with all requirements on transparency of its relationships with patient groups and listed all the groups supported on its website and thus any funding provided to Asthma UK was openly declared. Members of Asthma UK, including the named representatives, had participated in educational events for Novartis employees to highlight the importance of the company's medicines on the lives of patients with severe persistent allergic asthma. One of the named representatives of Asthma UK had also provided unpaid expertise at a Novartis advisory board.

Novartis stated that it routinely held educational events for a variety of conditions to educate and inform its employees on the importance of the work it did in developing medicines and the impact they could have for people with these conditions.

Novartis confirmed that it had a consultancy agreement as outlined in Clause 20 of the Code with the health professional quoted in the article. These included activities such as Novartis-sponsored medical educational events, symposia and advisory boards on severe asthma and allergy. The health professional was also an investigator on Novartis-sponsored clinical trials.

Novartis submitted that the pack shot shown in the article was not a UK pack for Xolair 150mg. The pack licensed in the UK had an ampoule containing 2ml solvent, whilst the one in the Daily Mail picture showed an ampoule containing 5ml of diluent. An internet search showed that the same pack photograph appeared on an independent website for the pharmaceutical industry. Novartis stated that this pack shot was not provided to the journalist or Asthma UK by either Novartis UK or by Novartis Switzerland. Furthermore, in 2012 this presentation (powder and solvent) was superseded by a new prefilled syringe. A copy of the current SPC for Xolair (powder formulation) was provided. Unfortunately, Novartis did not have a pack shot for the powder formulation so a copy of the pack artwork image was provided which it believed clearly showed how the pack differed.

For the reasons outlined above, Novartis considered that there was no breach of Clauses 22.1 and 22.2 of the Code in promoting prescription only medicines to the public. Consequently, Novartis did not consider that it had failed to maintain high standards or that it had brought discredit upon, or reduced confidence in, the pharmaceutical industry. The company thus denied breaches of Clauses 9.1 and 2.

Novartis hoped this information had assuaged concerns and provided the reassurance that Novartis continued to uphold high standards in its activities and actions.

**PANEL RULING**

The Panel noted that when complaints were received about what an independent journalist had published in the press, its rulings were made upon the material released by the company that might have prompted the article, not the article itself.

The Panel noted the time delay between the press release being issued (9, November 2012) and the publication of the article at issue (11, February 2013). The Panel further noted that although the press release was about a draft decision by NICE to revoke existing positive guidance on the use of Xolair in patients aged 12 and above, it did not otherwise appear to have influenced the content of the article in the Daily Mail. The article in the Daily Mail was principally one mother's story about her 14 year old son and how he might be affected by NICE's impending decision. The article concluded with a general discussion about the potential negative impact of the draft NICE recommendation on patient care. The article quoted a spokesperson from Asthma UK and also a hospital consultant in respiratory medicine. The article included a pack shot of Xolair which Novartis submitted was not a UK pack. The Panel noted that the press release did not refer to the 14 year old boy or provide any other case studies and although it quoted two hospital physicians, neither were the consultant quoted in the Daily Mail article. The press release did not refer to Asthma UK. The Panel noted Novartis's submission that neither it nor its PR agency had engaged with the author at any point over the story nor did it have any knowledge of the case study presented.

The Panel noted that the article was quite different to the press release; the press release had been issued three months before the article was published. The Panel noted the content of the press release and did not consider that it promoted Xolair to the public. No breach of Clause 22.1 was ruled.

The Panel noted that article stated that the effects of Xolair were 'unbelievable' and that it 'didn't cause terrible side-effects like other treatments'. In that regard the Panel noted that the tone of the press release was quite different and did not appear to have led to the strong, unequivocal claims in the article. The Panel thus ruled no breach of Clause 22.2.

The Panel considered that high standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel noted its rulings above and consequently ruled no breach of Clause 2.

**Complaint received** **14 February 2013**

**Case completed** **26 March 2013**

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CASE AUTH/2579/2/13

# GENERAL PRACTITIONER v BAYER

## Weblink to training workshop

**A general practitioner complained that he had had his time wasted by being misled into attending what he thought was a workshop to learn how to use the new EvoInserter, the insertion device for Mirena, an intrauterine contraceptive marketed by Bayer.**

**The detailed response from Bayer is given below.**

**The Panel noted that the Mirena on-line training material stated that one way to become familiar with the technique required to use the EvoInserter was to attend a Mirena training workshop. Delegates could find out about the workshops via the 'Mirena training workshop' link. The Panel noted Bayer's submission that such workshops were held in May/June 2012, leading up to the launch of the EvoInserter, and that as each workshop took place the date was removed from the website. The Panel noted, however, that all Mirena meetings throughout the year were accessed through the 'Mirena training workshop' link regardless of title or content. Health professionals were provided with a link to fulfil a specific training need (ie to learn how to use the EvoInserter) and so it was not unreasonable to assume that training dates/events offered through that link would fulfil that need. The Panel considered that the website was misleading in that regard and ruled a breach of the Code.**

**The complainant provided a copy of an email to him from the agency managing the logistics for the meeting which he had decided to attend. The email referred to the 'Mirena Education Programme' and a copy of the agenda was attached which detailed two presentations; 'What's topical in contraception' and 'How to optimise counselling in intrauterine contraception (workshop)'. Bayer submitted information to show that the complainant had been sent an invitation and agenda by post. This invitation stated that the programme aimed to give delegates the optimum opportunity for an educational experience with a view to: update on what was topical in contraception, a workshop on counselling women for intrauterine contraception and holding a local fitters forum to discuss current issues. The Panel considered that although the meeting incorporated a workshop, it was clear from both the invitation and the agenda that it would be about counselling, not the practical use of the EvoInserter. The Panel noted Bayer's submission that in any event, two of its employees had been at the meeting to demonstrate the EvoInserter from the promotional stand and that demonstrator Mirenas and models were available for practice.**

**The Panel noted that the meetings were aimed at current fitters. It might have been helpful if the agenda had made this point clear, particularly as the link to register for these meetings was the same as the link to meetings to learn how to use the EvoInserter. However, the Panel considered that the invitation and the agenda for the meeting at issue were clear as to the content and that once in receipt of these, the complainant should have realised that the meeting was not the training workshop he had imagined it to be. The Panel considered that in that regard the nature of the meeting had not been disguised. No breach of the Code was ruled.**

**The Panel did not consider that the circumstances meant that high standards had not been maintained. No breach of the Code was ruled.**

A general practitioner complained about a training workshop on Mirena (an intrauterine contraceptive containing levonorgestrel) organised by Bayer HealthCare.

**COMPLAINT**

The complainant noted that Bayer advertised a training workshop for health professionals to fit Mirena using its new EvoInserter. As the company was to provide the training, the complainant decided to attend the January training workshop in Leicester. The complainant noted that in an email from an events management agency to a GP colleague, dated 26 April 2012, it was stated 'The workshop will be led by a local trainer and delegates will be given the opportunity to use a demo EvoInserter'. The complainant noted, however, that no such hands-on training took place. The complainant considered that he had been misled in attending an event which he believed was training to fit Mirena using the new EvoInserter, but was not.

The complainant provided his email communication with the same events management agency. He noticed the title of 'Mirena Medical Education Programme' was different from the on-line title of 'Mirena training workshop'.

The complainant was not happy that Bayer had behaved improperly and wasted his time.

When writing to Bayer, the Authority asked it to respond in relation to Clauses 7.2, 9.1 and 12.1 of the Code.

**RESPONSE**

Bayer explained that in 2012 it introduced an improved insertion device, the EvoInserter, for the Mirena Intrauterine System (IUS). Mirena was the only IUS currently available in the UK. The changes were relatively minor and ergonomic. In granting the licence the Medicines and Healthcare products Regulatory Agency (MHRA) did not require Bayer to inform health professionals about the changes. However, Bayer developed a communication plan to inform health professionals about the new insertion device and used a variety of channels, including face-

to-face meetings and an on-line training programme. Bayer considered as the communications on the changes were about the benefits of the product, they were treated as promotional activities. Before the launch of the EvoInserter, Bayer also developed a series of promotional/educational meetings on Mirena which incorporated a workshop on the new inserter. Each workshop was led by health professionals who were experienced trainers in intrauterine techniques. Invitations to these events were sent in April 2012 and the meetings ran from 8 May to 19 June. The invitation and agenda for these meetings was provided.

Bayer submitted that practices and/or clinics tended to hold low numbers of Mirena as stock; consequently those individuals who fitted Mirena were likely to encounter the new inserter soon after it became available. All the training was therefore planned to take place before the EvoInserter was launched in June 2012. In addition to the meetings programme, an on-line training programme was available which was widely advertised and communicated to health professionals involved in family planning.

To attend a Mirena educational meeting heath professionals had to register via the Mirena website when the dates, locations and agenda were available.

Bayer stated that from the evidence submitted, a GP was forwarded, from a colleague, an email on 26 July 2012 which had originally been sent by Bayer in April 2012; the email outlined a meetings programme which included the EvoInserter workshop which had ended in mid-June 2012. As each meeting happened it was removed from the website thus if the recipient had gone on the Mirena website in July 2012 no meetings or workshop dates were listed.

Bayer ran a number of educational meetings/workshops, relevant to those health professionals who were involved in providing Mirena, throughout the year. Bayer's Spring/Summer meetings programme ended on 19 June, these included the EvoInserter workshops. From 11 October the dates of an Autumn/Winter meetings programme could be accessed from the website. All meetings throughout the year were accessed from the 'Mirena training workshops' link on the website but the specific title and content of each meeting series changed.

Invitations to the Autumn meetings programme were posted on 16 October and emailed (with permission) on 22 October. The agenda clearly stated the titles of the talks. The talks were relevant to those interested in contraception, in particular intrauterine contraception. The meetings were Mirena branded and all communication was accompanied by prescribing information. Furthermore, registration for the meetings could only be achieved by registering on the promotional website Mirena.co.uk. As there was no attempt to disguise the promotion of Mirena Bayer rejected the alleged breach of Clause 12.1.

The invitations were targeted at those heath professionals Bayer had identified as qualified to fit long acting reversible contraception (LARC) or intrauterine contraception (IUC) and all were sent the invitation by post. Bayer considered that these heath professionals specifically would be interested in the content of the meetings.

A leavepiece was also distributed via Bayer's sales force with a reply paid card to register interest.

Once someone registered interest in a meeting via the Mirena website, the events management agency Bayer contracted to handle the logistics of the meeting programme confirmed attendance by email. The agenda for the meeting was provided.

The Leicester meeting was originally scheduled for December but moved for logistical reasons. All those registered were informed of the postponement. The new date was communicated in early January and was again accompanied by the meeting agenda.

A final reminder to those registered was emailed the day before the meeting with directions to the venue and the agenda attached. Bayer provided a list of those who had attended the Leicester meeting and details as to how they were informed of the meeting. A separate list of when they registered to attend was also provided.

Bayer submitted that those who attended the Leicester meeting were sent the agenda on at least three occasions. The content of the meeting was clear from the agenda. There was no suggestion that there would be an EvoInserter training workshop, it was clearly stated that the subject of the workshop was on counselling in intrauterine contraception.

With regard to the lack of hands-on EvoInserter training which the complainant had wanted, Bayer noted that at the meetings held from November to January at least two of its employees were present and available to demonstrate the EvoInserter from a promotional stand. Demonstrator Mirenas (no active ingredient and clearly labelled) and model uteruses were available for anyone to practice with. Demonstration/training devices and uterus models could be requested and sent or delivered to any health professional who requested them. All of the speakers were experienced in intrauterine contraception and Faculty of Sexual and Reproductive Health accredited trainers in intrauterine techniques. Bayer submitted that there was ample time for discussion and questions on any topic including the EvoInserter. Discussion was encouraged at all of the meetings to share best practice amongst this group of health professionals who could fit intrauterine contraception.

Bayer stated that it held meetings with the same programme in 16 locations between November 2012 and January 2013 and 299 health professionals had attended. Bayer had reviewed the feedback forms from all the meetings and no-one rated the information received before and during the meeting as below expectation. Nationally most rated the

content as useful. The feedback forms for the Leicester meeting were provided.

Bayer stated that its employees who attended the Leicester meeting had confirmed that a number of the attendees were shown how to use the EvoInserter on the promotional stand. One employee remembered one doctor saying he/she thought there was going to be something about the EvoInserter; they declined an offer of a one-to-one demonstration and the chance to practice with the demonstrators available.

In Bayer's view, the basis of the complaint was a misunderstanding about an email forwarded by a colleague and the assumption that any meeting Bayer held many months later would have the same content. Additionally despite receiving the agenda on a number of occasions, which included the titles of the talks, the complainant did not realize the content was quite different to the meeting they assumed they were attending.

In summary, Bayer believe the promotional content of the meeting and the nature of the workshop was made very clear from the outset and there was no indication that the meeting would have specific trainer-led use of a demonstrator Mirena EvoInserter. Bayer believed the meeting had good educational content which was delivered by local experts and relevant to the invited audience. Feedback from the meetings was positive. Bayer therefore rejected the alleged breaches of Clauses 12.1, 7.2 and 9.1.

**PANEL RULING**

The Panel noted that the complainant provided a printed copy of the Mirena on-line training material which stated that the reader could familiarise themselves with the technique required to use the new insertion device, the EvoInserter, either by completing the on-line training module and/or by attending a Mirena training workshop. Delegates could find out about the workshops by clicking on the 'Mirena training workshop' link. The Panel noted Bayer's submission that such workshops were held between 8 May and 19 June 2012, leading up to the launch of the EvoInserter, and that as each workshop took place the date was removed from the website. The Panel noted, however, that all Mirena meetings throughout the year were accessed through the 'Mirena training workshop' link even though the specific title and content of each meeting series changed. The Panel noted Bayer's submission that registration for the meetings could only be achieved by registering on the Mirena website. In the Panel's view the arrangements were misleading. Health professionals were provided with a link to fulfil a specific training need (ie to learn how to use the EvoInserter) and so it was not unreasonable to assume that training dates/events offered through that link would fulfil that need. The Panel considered that the website was misleading in that regard and ruled a breach of Clause 7.2.

The complainant appeared to have decided to attend a Mirena training workshop based on an email originally sent to his colleague in April 2012 and forwarded to him on 26 July 2012 ie when the workshops had already finished. The email stated that 'delegates will be given the opportunity to use a demo EvoInserter'. The complainant also provided a copy of an email to him from the agency managing the logistics for the meeting which he had decided to attend. The email referred to the 'Mirena Education Programme' and the fact that the meeting he had elected to attend had been postponed until January 2013. A copy of the agenda was attached to the email which detailed two presentations; 'What's topical in contraception' and 'How to optimise counselling in intrauterine contraception (workshop)'. The Panel noted that Bayer had submitted a list of those who had attended the meeting and information to show that the complainant had been sent an invitation and agenda by post. The invitation to the Autumn series of the 'Mirena Medical Educational Programme' stated that the programme aimed to give delegates the optimum opportunity for an educational experience with a view to: update on what was topical in contraception, a workshop on counselling women for intrauterine contraception and holding a local fitters forum to discuss current issues. The Panel considered that although the meeting incorporated a workshop, it was clear from both the invitation and the agenda that it would be about counselling, not the practical use of the EvoInserter. The Panel noted Bayer's submission that in any event, two of its employees had been at the meeting to demonstrate the EvoInserter from the promotional stand and that demonstrator Mirenas (with no active ingredient) and model uteruses were available for delegates to practice with.

The Panel noted that the meetings were aimed at current fitters. It might have been helpful if the agenda had made this point clear, particularly as the link to register for these meetings was the same as the link to meetings to learn how to use the EvoInserter. However, the Panel considered that the invitation and the agenda for the meeting at issue were clear as to the content. The Panel noted its ruling above regarding the misleading link to Mirena meetings/events but considered that once in receipt of the invitation and agenda, the complainant should have realised that the meeting was not the Mirena training workshop he had imagined it to be. The Panel considered that in that regard the nature of the meeting had not been disguised. No breach of Clause 12.1 was ruled.

The Panel did not consider that the circumstances meant that high standards had not been maintained. No breach of Clause 9.1 was ruled.

**Complaint received** **20 February 2013**

**Case completed** **28 March 2013**

CASE AUTH/2582/2/13

# VOLUNTARY ADMISSION BY ROCHE

## Promotion before the grant of a marketing authorization

**Roche voluntarily admitted that an uncertified, promotional mailing for Perjeta (pertuzumab) had been sent to UK health professionals in February 2013, before it had received the relevant marketing authorization.**

**The detailed response from Roche is given below.**

**The Panel noted that the Perjeta mailing at issue had been distributed before Roche had received the marketing authorization which permitted the medicine's sale or supply. Copies of the mailing had been sent to the mailing house before it had been certified. The mailing house should have waited for confirmation from Roche that the material had been certified before distribution. The Panel noted, however, that in an email to the mailing house a Roche employee had asked 'In order to hit the target list on 19th Feb – when do you need the material?' There was no indication in the email that the date of 19 February was subject to confirmation.**

**The Panel noted Roche's submission that there was a contract between Roche and the mailing house and a standard agreed production process in place at the mailing house. The contract required the parties to establish a project confirmation and Roche to place a project brief with the agency. There was, however, no project confirmation between the company and its agency for the mailing at issue and no formal project brief.**

**The Panel noted that a Perjeta mailing had been sent to health professionals before the product had been granted a marketing authorization. A breach of the Code was ruled. The mailing was sent before it had been certified. A further breach of the Code was ruled.**

**The Panel noted that the mailing appeared to have been sent in error due to a combination of poor communication, contractual errors and human error; high standards had not be maintained. A breach of the Code was ruled.**

**In the Panel's view, companies must be extremely careful to ensure that material for new medicines were not distributed before the relevant marketing authorization had been received. Given the seriousness with which promotion before the grant of a marketing authorization was viewed, Roche's failure to follow set procedures and its reference to a mailing date without making it abundantly clear that the date was subject to confirmation, the Panel considered that the company, by promoting an unlicensed medicine had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.**

Roche Products Limited voluntarily admitted that it had promoted Perjeta (pertuzumab) before the medicine had been granted a marketing authorization to permit its sale or supply.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Roche.

**COMPLAINT**

Roche stated that on Thursday, 21 February 2013, an uncertified promotional mailing for Perjeta was sent in error by a third party mailing house to 2,260 UK health professionals.

Roche stated that it was committed to the appropriate use of medicines and protecting patient safety and strove to maintain high standards in the ethical promotion of its medicines. As such, the company and its employees understood the strict requirements of UK medicines regulations and the Code not to promote a medicine in the absence of its marketing authorization.

On discovery of this matter, Roche immediately tried to stop the mailing being posted. The matter was escalated to senior management and an investigation was undertaken to understand the root cause. Roche contacted the PMCPA for guidance as to what it could do to mitigate the risk of providing incorrect information to health professionals. The company also informed the Medicines and Healthcare products Regulatory Agency (MHRA).

Roche stated it was with deep regret that it acknowledged responsibility for the actions of the third party agency which acted on its behalf. The company voluntarily admitted breaches of Clauses 3.1, 9.1, 14.1 and 2.

Roche explained that the marketing authorization for Perjeta was expected in the first week of March. The mailing at issue was due to be sent after the marketing authorization was received, but as it was sent beforehand it clearly constituted promotion prior to the grant of a marketing authorization.

Roche explained that following artwork and proof approval of the job bag, it was company practice to print mailings with stock sent in parallel to the mailing house and to Roche for final certification. The mailing house had to await confirmation of certification from Roche before it distributed the mailing. This process was not followed and the mailing was distributed before the mailing house received this confirmation.

In failing to manage the effective implementation of this process and in acknowledgement of the human error of the mailing house, Roche accepted that it had failed to maintain high standards.

Given the seriousness of a breach of Clause 3, Roche considered that these actions risked reducing confidence in the industry and as such understood that a breach of Clause 2 might be a conclusion in this matter.

**RESPONSE**

Roche stated that the mailing with envelope (ref RXUKPERT00040c) and reply-paid card (RPC) (ref RXUKPERT00040d) were developed as part of a launch campaign for Perjeta, a new medicine for HER2-positive breast cancer, which at the time had not received its marketing authorization. The intended audience was oncologists, nurses and pharmacists with an interest in breast cancer.

The materials were certified on 18 January 2013 for submission to the MHRA for pre-vetting. As the pre-vetting materials were provided electronically, the materials were certified as PDFs specifically for the MHRA and watermarked 'MHRA draft'; this was to avoid confusion with the final production materials. The MHRA notified Roche on 24 January that it did not require any amendment to the mailing.

Roche's standard operating procedure (SOP) on approval and certification stated that permission to proceed to print was provided following the approval of a proof. Following notification from the MHRA, print production was commenced so that the mailing, envelope and RPC could be certified in their final forms. The reason for a full print run, rather than producing a small number of digital copies for certification, was that differences could occur between digital copies and those produced in a print run and as such they might not represent the final form.

Mailings (promotional or non-promotional) were printed and sent in parallel to Roche for final certification and to the mailing house for collation and labelling. The mailing house had to wait for email confirmation of final certification before it started the distribution process. There was a comprehensive contract between Roche and the mailing house and a standard agreed production process in place at the mailing house to confirm the mutual obligations of the two parties. Specific clauses highlighted the importance of ensuring compliance with the Code and respective legal obligations.

Clause 1.1 of the contract stipulated, *inter alia*, that for each project the parties would establish a project confirmation. Further, clause 2.1 stated that for each project, Roche would place a project brief with the agency. For the Perjeta mailing, in error on the part of Roche, no project confirmation was developed. There was also no formal brief, although an informal brief was provided by Roche to the mailing house in December 2012 which resulted in the mailing house providing Roche with some estimates.

An email on 17 January 2013 from Roche to the mailing house provided further detail of the project and included a postscript enquiry as to the latest date the material at issue needed to be with the mailing house in order to be distributed on 19 February – when it was anticipated that the marketing authorization for Perjeta would have been granted. Roche noted, however, that both the contract and agreed production process at the mailing house required that materials could only be released following confirmation from Roche of certification. A purchase order was raised on 22 January representing the official authorization by Roche for the agency to commence work on the project.

As part of the routine communication between Roche and the mailing house, a telephone call on 21 February confirmed receipt of the materials, review of the final mailing list and expected next steps. This call was returned 2 hours later, with the information that the mailing had been sent in error. An account of the telephone conversation was provided.

The promotional mailing for Perjeta was sent to 2,634 UK health professionals. Although the mailing had not been amended since it was certified for MHRA pre-vetting, it was not certified in its final hard copy form before it was distributed.

On discovery of this issue, Roche immediately tried to prevent the mailing entering the UK postal system. The matter was appropriately escalated to senior management. Roche contacted the PMCPA for guidance as to what it could do to appropriately mitigate the risk of providing incorrect information to health professionals and also contacted the MHRA.

An issues management group was instigated which consisted of senior UK managers and the respective heads of departments involved in the response. Evidence was gathered from the employee who originated the job and the third parties involved in the project.

A thorough stakeholder assessment was undertaken to ensure Roche had appropriately considered the possible routes of enquiry that might be initiated from the mailing. A plan of action for each stakeholder group was cross referenced with guidance provided by the PMCPA and confirmed by the issues management group.

Roche stated that a reactive statement and brief was certified and provided on 22 February (within 24 hours of the issue arising) for use by medical information, the supply chain customer service team and the communications department should any enquiries be received. Written briefs and reactive statements were certified and provided to field staff. These were emailed to all oncology field staff and a teleconference was convened with all field staff working in breast cancer to alert them to the brief and to direct them as to what to do if the matter was raised by a customer. This brief was reiterated in an email on 25 February to ensure appropriate direction was reinforced.

A reactive email and letter were generated to respond to any RPCs received from the mailing. The issues management group monitored the responses received from RPCs, medical information requests and product requests through the customer care group. Eight queries had been received to date.

A formal recall was initiated to ensure internal staff and agencies confirmed destruction or return of any remaining mailings. Field staff were instructed on what to do if a customer directly returned a mailing or the RPC.

Copies of all these documents were submitted.

Roche submitted that its investigation confirmed that although approval processes had been followed up to the point of distribution of the mailing, there were a number of contractual requirements between Roche and the mailing house that were not met in relation to the placing of a project confirmation and a formal brief; processes had not been followed by either the Roche employee involved or the mailing house. Communication had been received from the mailing house which identified that the mailing was released before certification because production staff failed to gain the required confirmation of certification in advance of distribution. In addition, Roche acknowledged the lack of a signed project confirmation form or formal brief and the failure for either side to confirm a target mailing date following enquiries regarding print and delivery requirements. Roche had taken steps with both its employee and the mailing house to address the failure to follow documented procedure.

The conclusion of the investigation was that human error and failure to follow agreed process led to the distribution of the mailings.

It had been recognized, and demonstrated by this incident, that sending materials to a third party for packing and distribution ahead of final certification exposed the company to a level of risk, despite agreed processes and contracts.

A group had been convened to review the internal process for mailings, although no formal change to the SOP would be made until the outcome of this case had been received. It was proposed that the internal process should be amended to ensure that, as with other printed materials, mailings, must be quarantined in the company's warehouse facilities and only released to a mailing house when they had been certified.

With regard to the requirements of Clause 3.1, Roche noted that the marketing authorization for Perjeta had not been received when the mailing was sent and Roche accepted that it had thus unwittingly promoted a medicine prior to the grant of its marketing authorization. An electronic form of the material had been certified as part of the MHRA pre-vetting process and, although the content had not changed, Roche accepted that the final form of the hard-copy mailing had not been certified in breach of Clause 14.1.

In failing to fully manage this process and in acknowledgement of the human error of the mailing house involved in this matter (acting on Roche's behalf) and of a Roche employee, Roche accepted that it had failed to maintain high standards at all times, in breach of Clause 9.1.

Given the seriousness of a breach of Clause 3.1 and with no dispute of the fact that this matter constituted promotion prior to the grant of marketing authorization, Roche considered these actions had risked reducing confidence in the industry and as such understood that a breach of Clause 2 would be a conclusion in this matter.

Roche reiterated that it was committed to the appropriate use of medicines and protecting patient safety and that it strove to maintain high standards in the ethical promotion of its medicines. As such, the company and its employees understood the strict requirements of UK medicines regulations and the Code not to promote a medicine in the absence of a marketing authorization.

Roche was committed to ensuring that such an issue could not happen again.

**PANEL RULING**

The Panel noted that the Perjeta mailing at issue had been distributed before Roche had received the marketing authorization which permitted the medicine's sale or supply. Copies of the mailing had been sent to the mailing house before it had been certified. The mailing house should have waited for confirmation from Roche that the material had been certified before it distributed the mailing. The Panel noted, however, that in an email to the mailing house a Roche employee had asked 'In order to hit the target list on 19th Feb – when do you need the material?' There was no indication in the email that the date of 19 February was subject to confirmation.

The Panel noted Roche's submission that there was a contract between Roche and the mailing house and a standard agreed production process in place at the mailing house. Clause 1.1 of the contract required the parties to establish a project confirmation; a template project confirmation form was provided which required a project overview and timeframes to be stipulated. Clause 2.1 of the contract required Roche to place a project brief with the agency. There was, however, no project confirmation between the company and its agency for the mailing at issue and no formal project brief - although the Panel noted Roche's submission that emails between the company and the mailing house constituted an informal brief.

The Panel noted that a Perjeta mailing had been sent to health professionals before the product had been granted a marketing authorization. A breach of Clause 3.1 was ruled. The mailing was sent before it had been certified. A breach of Clause 14.1 was ruled.

The Panel noted that the mailing appeared to have been sent in error due to a combination of poor

communication, lack of a project confirmation, no formal brief and human error. In the Panel's view high standards had not be maintained. A breach of Clause 9.1 was ruled.

The Panel noted Roche's submission that in the light of the events above, it had proposed that mailings would no longer be sent to mailing houses ahead of certification; they would instead be quarantined in the company's warehouse until they had been approved for release. The Panel agreed with Roche's acknowledgement that sending uncertified material to a mailing house exposed the company to the risk of the material being distributed ahead of time.

In the Panel's view, companies must be extremely careful to ensure that material for medicines which were awaiting authorization were not distributed before the relevant marketing authorization had been received. Given the seriousness with which promotion before the grant of a marketing authorization was viewed, Roche's failure to follow set procedures and its reference to a mailing date without making it abundantly clear that the date was subject to confirmation, the Panel considered that the company, by promoting an unlicensed medicine had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

**Complaint received** **27 February 2013**

**Case completed** **27 March 2013**

# CODE OF PRACTICE REVIEW – May 2013

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

| | | | | | |
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| **2554/11/12** | **Anonymous health professionals v Ipsen** | | **Breach Clause 9.1** | | |
| **2556/11/12** | **Anonymous health professionals v Janssen** | | **Breaches Clauses 9.1 and 19.1** | | |
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|---|---|---|---|---|---|
| **2563/11/12** | **Anonymous health professionals v Takeda** | **Sponsorship of a meeting** | **Breach Clause 9.1** | **No appeal** | **Page 85** |
| **2565/11/12, 2566/11/12 and 2567/11/12** | **Health professionals v Boehringer Ingelheim** | **Online survey** | **Breach Clause 9.1 in each case** | **No appeal** | **Page 105** |
| **2568/12/12** | **Voluntary admission by Astellas** | **Too many pages of advertising** | **Breach Clause 6.3** | **No appeal** | **Page 114** |
| **2569/12/12** | **Merck Sharp & Dohme v Novo Nordisk** | **Promotion of Victoza** | **Breach Clause 7.2** | **No appeal** | **Page 116** |
| 2571/12/12 | Anonymous health professional v Pharmacosmos | Symposium invitation | No breach | No appeal | Page 122 |
| **2577/2/13** | **Voluntary admission by Abbvie** | **Out-of-date prescribing information** | **Breaches Clauses 4.1 and 9.1** | **No appeal** | **Page 124** |
| 2578/2/13 | Journalist v Novartis | Daily Mail article | No breach | No appeal | Page 127 |
| **2579/2/13** | **General Practitioner v Bayer** | **Weblink to training workshop** | **Breach Clause 7.2** | **No appeal** | **Page 130** |
| **2582/2/13** | **Voluntary admission by Roche** | **Promotion before the grant of a marketing authorization** | **Breaches Clause 2, 3.1, 9.1 and 14.1** | **No appeal** | **Page 133** |

# PMCPA | 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, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed or electronic material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of three of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member does not participate and is not present when the Panel considers it.

Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, must be in a majority when matters are considered by the Appeal Board.

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.

Further information about the Authority and the Code can be found at www.pmcpa.org.uk

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria St, London SW1E 6QT

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.