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**