CASE AUTH/2721/7/14

SHIRE v GENZYME

Material for an advisory group

Shire Pharmaceuticals complained about material used by Genzyme Therapeutics in relation to a meeting of the Lysosomal Storage Disorders Expert Advisory Group (LSDEAG) on 26 February 2014. The material compared Genzyme's Fabrazyme (agalsidase beta) with Shire's Replagal (agalsidase alfa) both of which were indicated for long-term enzyme replacement therapy in patients with confirmed diagnosis of Fabry Disease.

The detailed response from Genzyme is given below.

Shire alleged that Genzyme used uncertified, factually incorrect, misleading, inaccurate and promotional information at the LSDEAG meeting. The meeting was instigated by Genzyme and was attended by health professionals, patient group representatives and senior NHS managers. Shire attended the meeting on the understanding that it was a non-promotional scientific exchange. Before the meeting, Genzyme circulated a written narrative, 'Genzyme proposal to NHS England for major cost savings in low dose maintenance Fabry patients currently treated with Replagal' and a version of the presentation entitled 'Fabry enzyme replacement therapy: Clarification of the science and the significant cost savings of our tender proposal'. The presentation given at the meeting contained a significant amendment on Slide 4 although this was not notified or clarified for the audience.

Genzyme's presentations 1 (pre-circulated) and 2 (used at the meeting) consisted of twenty two slides with the stated aim being to clarify the science for both Fabrazyme and Replagal. Genzyme stated that the presentation would also show the significant cost savings by a wholesale switch from Replagal to Fabrazyme.

Shire attended the meeting in response to an unsolicited request from the chairman of the LSDEAG. The request was generated in response to a solicited Genzyme meeting held with the chairman in late 2013. In a letter to Shire dated 27 May 2014, Genzyme stated that Shire was responsible for 'unfounded and incorrect rumours' that the low maintenance dose of Fabrazyme was 'unlicensed' or even 'illegal'. As a result of these rumours Genzyme sought to clarify the situation. Shire strongly refuted this unfounded allegation particularly as a basis for Genzyme's solicitation of the LSDEAG meeting and inappropriate actions during it.

Shire understood the LSDEAG meeting was intended to be a non-promotional presentation of the publicly available evidence of both Fabrazyme and Replagal. The stated purpose from Genzyme was that its presentation and narrative would clarify the science and the significant cost savings of its proposal in respect of Fabrazyme. Shire stated that in attempting to do this, Genzyme presented misleading and inaccurate information which was inconsistent with the Fabrazyme summary of product characteristics (SPC), promoted actions with the potential to adversely affect patient safety, presented misleading comparisons, made unsubstantiated claims of superiority over Replagal and promoted Fabrazyme in a setting which was intended to be non-promotional, particularly by presenting cost benefits to switch products, leading to disguised promotion and a failure to certify.

Shire noted that Genzyme repeatedly submitted that the LSDEAG was a 'national public organisation' but in reality it was an 'advisory group' which did not have a public constitution or a national public remit. The LSDEAG was thus not, in Shire's view, a 'national public organisation' in the sense intended by the Code, particularly as it was not a 'public' organisation in the same way that the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) or the Scottish Medicines Consortium (SMC) were. Even if it was, the material could only be exempt from the Code if it was factual, accurate and not misleading; this was not so; Shire also alleged that to present 'cost benefits' at such a meeting was promotional.

The Panel considered that the audience which included clinical experts as well as health professionals from specialised services, including commissioning and patient association representatives would be familiar with the products but this did not negate the need to ensure that materials were sufficiently complete, not misleading and in compliance with the Code. The Panel noted Genzyme's submission that whilst the clinical experts might be familiar with the studies they might be less familiar with regulatory processes and the specific intricacies related to ultra-rare diseases such as conditional licences and acceptable burdens of proof. The Panel noted that the Code stated, *inter alia*, that the term promotion did not include:

- **information supplied by pharmaceutical companies to national public organisations, such as the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) is exempt from the Code provided the information is factual, accurate and not misleading.**

The Panel first had to consider whether the Genzyme material could take advantage of two potential exemptions. In this regard, the Panel had to consider how the meeting arose, the parties understanding about its content and the status of LSDEAG.

The Panel noted Genzyme's submission that it had been invited to present scientific evidence at the meeting to address questions and comments

regarding the 0.3mg/kg Fabrazyme dose arising following the conclusion of the 2012 tender process; the material would have a direct impact on treatment guidelines that LSDEAG drew up following the tender. The Panel noted that the content of the narrative and presentations appeared to be broader than such matters. As stated by Genzyme, the material covered the differences between the products in relation to dose, price per milligram, the precise regulatory status of various doses and the implications of these points on the cost per patient. The material provided by Genzyme showed that the meeting organiser did not refer to any cost implications of interchanging products whereas cost savings were referred to in the narrative title and included throughout. The Panel had no way of knowing what was discussed during telephone conversations, a pre-meeting or the meeting. The Panel considered that, contrary to Genzyme's submission, generally the tender process would be considered promotion of the medicine in question.

The Panel noted that the Code defined promotion as 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. The Panel did not consider that it had been established that the activity amounted to responding to an unsolicited enquiry; Genzyme initiated the sequence of events that led to the meeting and it appeared that the presentations and narrative might have gone beyond the original ambit of the meeting as evidenced by the email from LSDEAG. In any event, any response to an unsolicited enquiry had to be non-promotional and, in this regard, the Panel noted its comments above about the promotional nature of the tendering process. In the Panel's view, the meeting was inextricably linked to matters arising from the original tender process and the scope and content of the material and the emphasis on comparative costs was such that it appeared to be promotional. In the Panel's view, Genzyme could not take the benefit of the exemption to the definition of promotion in the Code for responses to unsolicited enquiries.

The Panel noted the submissions regarding the status of the LSDEAG which was not given as one of the examples of public bodies in the Code. The examples, NICE, AWMSG and SMC all had a role in health technology appraisal. The list was not comprehensive. The Panel queried whether the role of LSDEAG when providing advice at the request of the Specialised Services Commissioning Function (SSCF) to NHS England was sufficiently similar to NICE, AWMSG and SMC. The Panel noted that, according to Genzyme, the minutes of the meeting bore the NHS England logo. The position was unclear. The Panel noted that the exemption in the Code only applied if the information provided to the public body was factual, accurate and not misleading. This latter point would need to be considered in relation to the detailed allegations.

The Panel noted that even if the material in question could take the benefit of an exemption to the definition of promotion as submitted by Genzyme, the material did not fall outside the scope of the Code. It still had to comply with certain aspects of it.

The Panel was concerned that Genzyme's narrative stated that 'These very similar proteins fall well within regulatory definitions of biosimilar in all pre-clinical studies' whereas in its response Genzyme submitted that it was very careful to explain, when introducing the word, in the material that the term was used in its general sense and not to imply that regulatory review had taken place.

The Panel noted that Shire had made detailed allegations regarding presentation 1 and included references to presentation 2 and the narrative. The meeting organiser had circulated the narrative and presentation 1 to attendees. Genzyme was aware of this when it provided the materials.

The Panel noted Genzyme's submission that the scientific presentation was not a comprehensive promotional piece designed to be 'standalone' and the detail was clearly laid out in the narrative. The Panel noted that the presentation and narrative should, nonetheless, be capable of standing alone as regards accuracy etc. In general, claims should not be qualified by the use of footnotes and the like. Although the narrative might have assisted understanding, it was not sufficient to qualify the presentations. The Panel considered that it was difficult to argue that Genzyme was not promoting its product at the meeting.

Upon appeal by Genzyme the Appeal Board first decided that as the material at issue included product claims and information on costs it met the broad definition of promotion. The matter for consideration was whether the material could take the benefit of the exemption to the definition of promotion for information supplied to national public organisations such as NICE, AWMSG and SMC which was factual, accurate and not misleading. The Appeal Board noted the two elements to the exemption. The Appeal Board noted that the material at issue was provided to the LSDEAG not the Specialised Commissioning Team (SCT). Neither the LSDEAG nor the SCT were included in the examples of public bodies listed in the Code. The Appeal Board noted that the list was not exhaustive and that other closely similar bodies might be recognised as national public organisations. Nonetheless, the Appeal Board considered that the exemption should be narrowly construed. The Appeal Board noted that all three bodies listed had a role in health technology assessment. The LSDEAG was established in 2005 to advise the chairman in his role and provide medical input to commissioning. The decisions of the bodies listed in the Code were publicly available and the minutes of the LSDEAG could only be publicly sourced via a freedom of information request. The Appeal Board considered that the LSDEAG/SCT were fundamentally different to those bodies listed in the Code. The Appeal Board noted that unlike the organisations listed in the Code the SCT had commissioning powers. The procurement role of the SCT was an important consideration as was the fact that the meeting was at Genzyme's request as part of the tender process. The Appeal Board considered all the circumstances and decided that the SCT/LSDEAG

was not sufficiently similar to the examples cited in the relevant exemption and thus could not take the benefit of that part of the exemption for national public bodies such as NICE etc.

As set out below, Shire made detailed allegations about many slides. Firstly, Shire made general allegations about biosimilarity and also alleged that the data cited were unable to support the claim of biosimilarity.

The Panel considered that the term biosimilar would be taken in the regulatory sense rather than in the general sense as submitted by Genzyme. The narrative stated 'Without exception, direct comparisons of the molecular properties of the two Fabry enzyme replacement therapies (ERT) demonstrate milligram for milligram equivalence (biosimilarity)', 'These very similar proteins fall well within regulatory definitions of biosimilar in all pre-clinical studies' and 'Despite the biosimilarity, the products have very different standard doses at 1.0mg/kg for Fabrazyme and 0.2mg/kg for Replagal; this strange situation is not replicated by any other biosimilar or generic medicines'.

The Panel noted the EMEA requirements for authorization of biosimilar medicines; studies needed to be carried out to show that the medicine was similar to the reference medicine and did not have any meaningful quality, safety or efficacy differences from the reference medicine . No such studies for Fabrazyme and Replagal had been performed and it was thus misleading and inaccurate and unsubstantiable to describe the two as 'biosimilar'.

With regard to Slide 3, the Panel ruled breaches of the Code which were upheld on appeal by Genzyme as the use of the term 'biosimilar' was misleading and thus the comparison was misleading. The Panel considered that its ruling on this point also applied to other slides. The Panel's rulings of breaches were upheld on appeal from Genzyme.

The Panel did not consider that the lack of information regarding the different methods of production and a complete picture of the information presented in the two products' EPARs was misleading as alleged. The Panel ruled no breach of the Code in this regard. The Panel noted that whilst the three statements on Slide 3 were not misleading, they did not substantiate the claim of biosimilarity in the heading of the slide as alleged. A breach of the Code was ruled which was upheld on appeal by Genzyme.

With regard to Slide 4, Shire referred to the differences in wording between the pre-circulated presentation and that presented at the meeting.

Shire alleged that the statement of 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg' was not consistent with the Fabrazyme SPC.

Shire noted that the Genzyme slide stated that the 'US licence application unsuccessful again'. This comment related to Shire withdrawing the US licence application on 14 March 2012. These comments were irrelevant to the UK market but were in any event misleading and disparaging as they inferred that the FDA had Replagal withdrawn after multiple attempts by using the word '…again'.

The Panel noted Shire's allegation that 'the long term clinical relevance has not been established' in relation to the reduced maintenance dose of Fabrazyme (0.3mg/kg) was omitted from Slide 4 in presentation 1 which was received by all of the delegates. The revised version which was presented on the day (presentation 2) contained the above phrase, however, it was not circulated as a replacement to presentation 1 and no disclosures were made on the day about the amendment.

The Panel noted the SPC wording:

> **'Posology**
>
> **The recommended dose of Fabrazyme is 1mg/kg body weight administered once every 2 weeks as an intravenous infusion.**
>
> **Alternative dosing regimens have been used in clinical studies. In one of these studies, after an initial dose of 1mg/kg every 2 weeks for 6 months, 0.3mg/kg every 2 weeks may maintain clearance of GL-3 in certain cell types in some patients; however, the long term clinical relevance of these findings has not been established (see section 5.1).'**

The Panel noted that the narrative gave more detail about the differences between the dosing of the products and the original licences which Genzyme stated were granted in exceptional circumstances for both products. The licences included specific obligations to provide data on long-term clinical outcomes. According to Genzyme, these had been fulfilled with Fabrazyme 1mg/kg but not Replagal 0.2mg/kg. Genzyme stated in the narrative that the caveat in respect of Fabrazyme 0.3mg/kg simply mirrored the continued provisional licence status of Replagal 0.2mg/kg 'in the absence of clinical outcome data approved as sufficient by the regulators'. Fabrazyme's full European licence following fulfilment of all the original specific obligations including submission of Phase IV data showing reduction of the rate of clinical events which Genzyme stated validated the efficacy of 1mg/kg. The narrative stated that in contrast the failure to meet the specific obligations for Replagal led to the EMA announcement on 25 April that the product was included on the list of products requiring additional monitoring and the need for a black triangle. The Panel noted that Shire's allegation related to the slides not the narrative.

The Panel considered that by failing to mention that the long-term clinical relevance of the reduced maintenance dose of 0.3mg/kg had not been established meant that Slide 4, presentation one was misleading, incapable of substantiation and was not sufficiently complete to enable the recipients to form their own opinion of the therapeutic value of the medicine. The Panel thus ruled breaches of the Code which were upheld on appeal by Genzyme.

In addition, the unqualified statement 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg' on Slide 4, presentation 1 was not consistent with the dosage particulars in Section 4.2 and efficacy details at Section 5.1 of the SPC. The Panel ruled a breach of the Code which was upheld on appeal by Genzyme.

The Panel considered the prominent statement 'US licence application unsuccessful again' implied that the FDA had rejected the Replagal application again which was misleading, inaccurate and disparaging. The Panel ruled breaches which were upheld on appeal by Genzyme.

Shire noted that on Slides 6 and 22 Genzyme compared the prices of Fabrazyme 1mg/kg, Replagal 0.2mg/kg to Fabrazyme 0.3mg/kg and alleged that this was not consistent with the Fabrazyme SPC.

The Panel considered that the Fabrazyme SPC was clear that the recommended dose was 1mg/kg body weight. The reference to the use of alternative dosing regimens in clinical studies was in relation to one of these studies when after an initial dose of 1mg/kg every two weeks for 6 months, a dose of 0.3mg/kg every two weeks might maintain clearance of GL-3 in some patients. The Panel further noted the SPC statement that the long-term clinical relevance of these findings had not been established. The Panel noted its comments above at about the 0.3mg/kg dose.

The Panel noted that the only dose cited in the posology section of the Replagal SPC 0.2mg/kg body weight. The Panel considered that the slides implied that Replagal and Fabrazyme at 0.3mg/kg had similar status according to the respective SPCs and this was not so. Insufficient information about the status of the 0.3mg/kg dose had been given. The Panel considered that the depiction of the 0.3mg/kg dose was inaccurate given the detail in the Fabrazyme SPC. The impression given was misleading and inconsistent with the SPC. The Panel ruled breaches of the Code which were upheld on appeal by Genzyme.

Slide 7 headed 'Sakuraba *et al*: Minimal differences in glycosylation except M6P – the ligand' reproduced table 1 from Sakuraba *et al* (2006) which compared the monosaccharide analysis from that study and Lee *et al* (2003). Data for mannose-6-phosphate (M6P) for Replagal and Fabrazyme were circled. Shire noted that no additional background to the type and purpose of the study eg that it was *in vitro*. A table taken directly from the publication was modified and only one set of values that differed between the two products were highlighted. Shire alleged that Genzyme had 'cherry-picked' the data. Sakuraba *et al* was not specifically about glycosylation and should not be used independently to substantiate the claims on the slide. No study limitations or caveats were mentioned.

The Panel considered that the audience would be clear that the data derived from *in vitro* testing.

The Panel noted that the table was taken directly from the publication. The only modification by Genzyme was that the data for mannose-6-phosphate was circled as Genzyme submitted this was the specific ligand which enabled cellular internalisation. Values for galactose, fucose, mannose, N-acetylglucosamine and sialic acid although not circled were included. The Panel did not consider that Genzyme had 'cherry-picked' data as alleged. The Panel queried Genzyme's submission that it had attached no significance to the possible differences: there appeared to be no other reason for highlighting and comparing the M6P results. Indeed, such differences were mentioned in the narrative which made the theoretical basis of the discussion clear. The Panel had no way of knowing precisely how the slide was presented. The slide had to be capable of standing alone. The Panel did not consider the slide misleading due to the highlighting of the M6P data. It appeared that Genzyme had a cogent reason for selecting that outcome. No breach of the Code was ruled. The Panel noted that no study limitations or caveats related to the table were given on the slide but did not consider that this necessarily rendered the table misleading as alleged. Shire had not established that the study caveats etc should have been included on the slide. The Panel ruled no breach. The Panel considered that the table was capable of substantiation and ruled no breach.

Slide 8 was headed 'Lee *et al*: Replagal is not more potent' and showed graphs of resonance units against protein concentration and mean response against activity for both products with regard to M6P binding and fibroblast update. Slide 9 headed 'Sakuruba [sic] (2006): Any potency differences favoured Fabrazyme' compared enzyme activities and M6P content for both products and stated that there was no difference in stability in plasma. Animal results favoured Fabrazyme.

Shire submitted that Genzyme appeared to link the potency claims with a claim of greater cost effectiveness. However, the cost effectiveness claim was itself misleading, meaning that the use of potency claims could not be justified.

Shire noted that Lee *et al* (2003) was cited with no additional background information on study design and type. Only two graphs were presented and missed vital context in order to fully interpret the data. The study was not powered to compare potency and the results showed no difference in enzyme activity between Replagal and Fabrazyme which had not been appropriately presented. The study did not substantiate the claim of potency and so was not clinically relevant and was misleading. No study limitations or caveats were mentioned.

Slide 9 was designed to highlight potency differences in the products but described only limited information about the study. The presentation did not mention that not all animal tests were completed with Replagal due to the limited quantity available to test and therefore did not substantiate the claim that 'animal results favoured [Fabrazyme]'.

Shire alleged that these results were 'cherry-picked' and Genzyme had omitted data showing the

additional differences between the two products. Presenting these data without qualifications was misleading and unbalanced.

The Panel noted that neither Slide 8 nor 9 referred to cost or cost effectiveness; it thus failed to understand Shire's allegation. Slide 6 showed annual costs but did not mention cost effectiveness. Shire might have been attempting to make a general point that the statements regarding potency and the similarity between the products reinforced Genzyme's data regarding the cost comparison of Fabrazyme 0.3mg/kg with 0.2mg/kg Replagal. However, there was no such link on the slides. The narrative discussed potency in relation to the products' similarity, not their cost-effectiveness. The Panel ruled no breaches of the Code in relation to Slides 8 and 9.

The Panel considered that Slides 8 and 9 were not designed to evaluate potency *per se*. Slide 8 did not claim superior potency only that Replagal was not more potent. Slide 9 stated that if there were any potency differences these favoured Fabrazyme. The Panel noted that the final bullet point on Slide 9 stated that 'animal results favoured [Fabrazyme]'. The Panel queried whether it was sufficiently clear that Slides 8 and 9 related to *in vitro* data and the clinical effects were not being compared. There was no clinical data to substantiate a claim that Fabrazyme was more potent than Replagal. The slides were misleading in this regard and breaches were ruled which were upheld on appeal by Genzyme. The Panel ruled a breach as the graphs on Slide 8 were not presented in such a way as to give a clear, fair, balanced view of matters which was upheld on appeal by Genzyme. The Panel ruled no breach of the Code with regard to Slide 9 as there was no artwork on that slide.

The Panel did not consider that either Slide 8 or Slide 9 constituted disguised promotion as alleged and ruled no breach of the Code.

Slide 11 headed 'Vedder *et al* (2007): The only attempted comparison of 0.2mg/kg vs 0.2mg/kg'. The slide included a graph comparing Fabrazyme 0.2mg/kg, Fabrazyme 1mg/kg and Replagal 0.2mg/kg in relation to decrease of LysoGb3 activity. It also included the quote 'Although the number of patients is small, it is unlikely that large differences in clinical potency exist at equal dose' and referred to van Breemen *et al* (2011).

Shire stated that Vedder *et al* was a small head-to-head study and included an off-label dose of Fabrazyme 0.2mg/kg. The Panel accepted that the data might be interesting from a scientific view point but considered as it used an unlicensed dose of Fabrazyme it was misleading and inconsistent with the SPC. Thus the Panel ruled breaches of the Code which were upheld on appeal by Genzyme.

Slide 12 headed 'Smid *et al* (2011) supply shortage' featured a graph which referred to changing Fabrazyme 1mg/kg to Replagal 0.2mg/kg fortnightly or Fabrazyme 0.5mg/kg monthly in relation to LysoGb3. Beside the graph was the statement 'Consistent with biosimilarity and equivalent pharmacodynamic dose response'.

Slide 13 headed 'Switch study after recent FDA Replagal withdrawal' referred to 15 male patients switched from Replagal 0.2mg/kg to Fabrazyme 1mg/kg in whom LysoGb3 decreased by 39.5% p=0.0002. It also included 'An increased pharmacodynamic response with an increased dose of biosimilar ERT' [Enzyme Replacement Therapy]. The slide was referenced to Barranger *et al* (2014).

Shire noted that neither Smid *et al* (2011) nor Barranger *et al* (2014 unpublished) were designed to compare the products to indicate biosimilarity or equivalent pharmacodynamic dose response and were therefore used in a misleading manner. The doses used in Smid *et al* were inconsistent with the product licence. The graph on Slide 12 was not clear and the results shown were only for male patients, consisting of half the patient population at the start and Genzyme did not provide any study detail or balanced safety information.

Both slides showed switching studies that were conducted during the Fabrazyme global product shortage. The full detail of potential risk of switching patients to a lower dose of Fabrazyme was not made explicit in the presentation with regard to adverse events. The European Medicines Agency Assessment Report (EMEA/H/C/000370, 9 July 2010), on the consequences of the shortage concluded that as more patients were prescribed lower doses of Fabrazyme, more adverse events were reported, and subsequently patients were moved to Replagal or to 1mg/kg of Fabrazyme.

Slide 13 included '… after recent FDA Replagal withdrawal'; Shire alleged that these comments were misleading and disparaging by inferring that the FDA had Replagal withdrawn. Shire had decided to withdraw the application.

The Panel noted that Slide 12 presented data following either changes in the dose of Fabrazyme or a switch to Replagal. These changes were a result of a supply shortage of Fabrazyme which according to Smid *et al* was due to viral contamination at Genzyme's production facility in June 2009 which led to a world-wide shortage and led to involuntary dose reductions or switch to Replagal. Slide 13 referred to the withdrawal of Replagal by Shire from the FDA approval process.

The Panel noted that the doses illustrated on Slide 12 were inconsistent with the Fabrazyme SPC. The Panel noted the EMA involvement regarding lowering the dose of Fabrazyme due to the supply shortage. It considered that this did not necessarily override the SPC. The Panel noted the promotional nature of the meeting. The reference to the unlicensed dose of Fabrazyme 0.5mg/kg monthly was inconsistent with the SPC as alleged. A breach was ruled which was upheld on appeal by Genzyme.

The Panel did not consider it was in itself misleading to show only the male patients. The patient population was 17 patients, 14 males and 3 females. There was no statistically significant difference in LysoGb3 increase after one year for females (p=0.3) whereas there was for males (p=0.001). This data was from a subset of patients. The Panel ruled no breach of the Code on this narrow point.

With regard to the alleged failure to provide safety data the Panel noted Smid's comments about that data and the EMA Assessment Report 2010. The Panel noted that the slide had to be capable of standing alone. The Panel considered that as Slide 12 did not provide information on safety, it was not balanced or based on an up-to-date evaluation of all the evidence. A breach of the Code was ruled, which was upheld on appeal by Genzyme.

With regard to Slide 13 the Panel noted again no safety data in relation to the consequences of switching. This study, Barranger *et al*, related to changing Replagal patients to Fabrazyme 1mg/kg. On balance, the Panel decided that Slide 13 was not similar to Slide 12 which referred to switching Fabrazyme 1mg/kg to Replagal 0.2mg/kg fortnightly or Fabrazyme 0.5mg/kg monthly. Shire had not identified the safety consequences in relation to a switch to Fabrazyme 1mg/kg. The Panel therefore ruled no breach of the Code in relation to Slide 13.

The Panel noted its rulings in relation to Slide 12 and considered that consequently the graph failed to satisfy the Code and a breach was ruled which was upheld on appeal by Genzyme.

The Panel noted that Slide 13 was headed 'Switch study after recent FDA Replagal withdrawal' and considered that it was not sufficiently clear that Shire had withdrawn its application. A breach of the Code was ruled. Given the audience and the purpose of the meeting of the Panel also considered that the phrase disparaged Replagal. A breach of the Code was ruled. These rulings were upheld on appeal by Genzyme.

Slide 15 headed 'Phase IV study of events ~50% risk reduction (conditional licence commitment)' compared event rate in the intention to treat population against time for Fabrazyme vs placebo. Shire stated that the graph detailed the number of 'events' (not labelled as adverse events) in patients receiving either placebo or Fabrazyme. The study and graph were not referenced, no dose was provided and no information regarding the actual adverse events to allow for an informed, clear and transparent risk assessment.

The Panel queried whether the impression given by the slide which referred to 'risk reduction' and 'event rate' would be interpreted by the audience as defined clinical events indicating deterioration of disease as submitted by Genzyme given the absence of any such reference on the slide.

The Panel ruled that the slide was misleading as insufficient information had been provided to give a clear summary of the data in breach of the Code which was upheld on appeal by Genzyme. No reference had been provided on the slide and the Panel ruled a breach of the Code which was upheld upon appeal by Genzyme.

Slide 16 was headed 'Mehta A, Lancet (2009) depicts rates of decline of renal function for enzyme replacement therapies' Shire stated that a graph from Mehta *et al* was presented with no clear contextual information. Shire alleged it was misleading not to state that the data was from a Fabry Outcome Survey (observational database) and this omission did not allow the audience to correctly interpret the data.

A separate Fabrazyme Phase III open label extension study was referenced in the graph using dashed lines. Replagal 0.2mg/kg data was also included but with no reference. The graph presented did not have clear information as to the sources for each bar that were included as part of the original Mehta publication. Shire alleged that this data was therefore 'cherry-picked' to show misleading information and unbalanced.

The Panel ruled a breach as no reference was included on the slide for the Replagal data and this was upheld upon appeal by Genzyme. The Panel considered it would have been helpful to include details about the nature of the data and in this regard the slide was misleading. A breach was ruled which was upheld on appeal by Genzyme. The Panel did not consider that Shire had provided sufficient detail in order to establish that there had been a breach of the Code in relation to its allegation about 'cherry picking' data and ruled no breach.

Shire noted that Slide 17 referred to Fabrazyme 0.2mg/kg/every other week, Replagal 0.4/kg/ every other week and Replagal 0.2mg/kg/weekly which were inconsistent with the Fabrazyme and Replagal SPCs.

Slides 18 and 19 showed two different graphs which Shire stated were unreferenced, unclear and did not provide clear context. The first showed a change in podocyte GL3-score vs cumulative agalsidase dose. The second graph showed the change in podocyte GL3-score vs the change in albumin-creatinine ratio. Shire alleged that the use of such graphs without context was misleading as the study was not powered to compare the efficacy and safety between Fabrazyme and Replagal.

Shire alleged that the information provided on Slides 17-19 did not substantiate the conclusions made on Slide 20. The study was not designed to provide the outcomes presented but were only observations made by the authors during the study thus rendering the Genzyme conclusions misleading.

The Panel ruled that Slide 17 was misleading and inconsistent with the SPC regarding the licensed doses of the two products. Breaches of the Code were ruled which were upheld on appeal by Genzyme other than one of the Panel's rulings. The Appeal Board considered that as the data was derived verbatim from its cited reference Tondel *et al*, and without any additional comment, Slide 17 could be substantiated and thus on this very narrow ground it ruled no breach of the Code. The appeal on this point was successful.

Slides 18 and 19 did not include any context. The Panel noted Genzyme's submission that the data was used to demonstrate similar milligram to milligram potency. The Panel considered that Slides

18 and 19 were contrary to the licensed doses and misleading. There was no reference on either slide. Each was ruled in breach of the Code and these rulings were upheld upon appeal by Genzyme.

The Panel noted its rulings above on Slides 18 and 19 and Shire's allegation that these slides did not substantiate the conclusions on Slide 20. The Panel noted that Slide 20 did not reflect the relevant caveats within the study. The Panel ruled that Slide 20 was misleading as alleged and this ruling was upheld on appeal by Genzyme.

Slide 21 headed 'My conclusions are:' set out a number of conclusions including that the proteins were biosimilar on a mg for mg basis in all published data, that the clinical data and licensed situation was more robust for Fabrazyme 1mg/kg but difficult and incomplete for both. The slide also stated that there were no published data which 'gainsay biosimilarity' and that the 'cost savings of switching low dose patients are compelling'.

Shire alleged that the claim on Slide 21 that 'Fabrazyme (0.3mg/kg) provides 50% more protein' misleadingly implied that Fabrazyme was superior to Replagal. This claim was not clinically relevant, was a hanging comparison, unbalanced and was not referenced. The slide also stated (in a larger font than that used in the rest of the presentation): 'Cost savings of switching low dose patients are compelling'.

Shire alleged that Genzyme's clearly intended to promote Fabrazyme by making unsubstantiated disguised promotional claims that Fabrazyme was more cost effective and to make misleading claims that the Fabrazyme data was more robust than that for Replagal. The assumptions made in an economic evaluation must be clinically appropriate. Shire alleged that the use of such claims in a non-promotional setting was in breach of the Code.

Shire submitted that Genzyme's assumptions were clinically incorrect and inconsistent with the Fabrazyme licence because the cost comparison was based upon the statement that all patients would be started and maintained on the 0.3mg/kg dose of Fabrazyme. No patients should be started on a 0.3mg/kg dose and this was only acceptable as a maintenance dose for some patients and should not be generalised for all patients.

Given that the cost comparison was inappropriate and that the comparison between Replagal and the reduced Fabrazyme dose was not capable of substantiation, Shire alleged that the presentations 1 and 2 were misleading, disparaging, inconsistent with the SPC and in breach of the Code.

The Panel noted the comments previously made regarding the licensed dosage and ruled breaches of the Code in relation to Slide 22.

The Panel was concerned that the conclusion 'Cost savings of switching low dose patients are compelling' on Slide 21 was misleading. This was compounded by Slide 22 headed 'ERT annual cost per 70kg patient at licensed dose'. The Panel noted that no account had been taken of the need to use 1mg/kg dose of Fabrazyme for six months before any consideration could be given to lowering the dose to 0.3mg/kg in certain patients and that the long-term clinical relevance of these findings had not been established. The Panel considered that Slide 21 was misleading in this regard and ruled breaches of the Code which were upheld on appeal by Genzyme.

The Panel did not consider it was sufficiently clear whether the phrase 'clinical data and licensed situation are more robust for Fabrazyme 1.0mg/kg but difficult and incomplete for both' referred to Fabrazyme 0.3mg/kg or Replagal or both. It noted its previous comments about the use of Fabrazyme 0.3mg/kg. Breaches of the Code were ruled which were upheld on appeal by Genzyme.

The claim that 'Fabrazyme 0.3mg/kg provides 50% more protein' was not clear as to what was being compared as alleged. The Panel ruled breaches of the Code which were upheld on appeal by Genzyme.

The Panel noted the promotional nature of the activity and did not consider that Slide 21 was disguised promotion. No breach of the Code was ruled.

With regard to the Genzyme narrative, Shire noted the statement that '… the pre-clinical and clinical data indicate that patients who are currently stable on low dose ERT (Replagal 0.2mg/kg) may be switched to Fabrazyme at a dose of 0.3mg/kg)'. There were no published data showing the clinical benefits in switching stable patients from Replagal to 0.3mg/kg Fabrazyme. There was no correlation between the dose of different medicines and their clinical effect. Genzyme was not encouraging the rational use of a medicine in proposing that patients stable on Replagal were switched to 0.3mg/kg Fabrazyme. No balance was given by Genzyme to information concerning Fabrazyme's benefits and the risks associated with its use at this dose.

The Panel noted its comments about the nature of the meeting. It also considered its rulings above regarding the presentation were relevant to the narrative.

The Panel noted both companies agreed there was no published data on the clinical benefits of switching patients from Replagal to Fabrazyme 0.3mg/kg. The narrative did not include the qualifications given in the SPC. The Panel considered the narrative was misleading and breaches of the Code were ruled which were upheld on appeal by Genzyme. The Panel also ruled breaches of the Code due to the lack of clinical data to supporting a switch and as the material did not encourage rational use, which were also upheld on appeal by Genzyme.

The Panel noted that Shire had not identified what, in its view, needed to be referenced in the narrative and nor had it provided sufficient detail with regard to an allegation of disparagement. No breach of the Code was ruled.

Shire stated that Genzyme had solicited a meeting with key stakeholders in sensitive commissioning roles within the NHS; the meeting was intended to be non-promotional. However, under the guise of providing a platform for a scientific debate, Genzyme knowingly promoted Fabrazyme by providing cost information. It also provided incorrect and misleading information which had not been certified.

Shire submitted that meeting attendees had expected a scientific discussion but instead received promotional information about Fabrazyme and how much cheaper it would be compared with Replagal. The inclusion of direct cost comparisons and switch proposals based upon unfounded biosimilarity claims rendered Genzyme's actions misleading, inaccurate and disguised promotion.

Shire alleged that due to the significant breaches outlined above Genzyme had failed to maintain high standards and had discredited the industry. Shire noted that in particular the potential risks posed to patients by promoting the wholesale switch between the products on the basis of inconsistent claims which were not supported by robust clinical or supportive data. Shire alleged a breach of Clause 2.

The Panel noted its comments above and that as the material was promotional it needed to be certified and this had not happened; high standards had not been maintained. Breaches of the Code were ruled which were upheld on appeal by Genzyme.

The Panel noted that Clause 2 was reserved for use as a sign of particular censure. The Panel noted the purpose of the meeting, including that it was to clarify information provided during a tender process and that the audience included experts in the field. The Panel was concerned that Genzyme had decided the material was non-promotional. The Panel also noted its rulings above that the material presented and pre-circulated was misleading, inconsistent with the Fabrazyme SPC and disparaging. On balance, the Panel considered that the circumstances brought discredit upon, and reduced confidence in, the pharmaceutical industry and thus ruled a breach of Clause 2.

Upon appeal by Genzyme the Appeal Board was astonished that Genzyme had considered that material provided subsequent to and directly related to a tender process was non-promotional. The Appeal Board was very concerned that regardless of whether Genzyme thought it could rely upon the exemption in Clause 1.2 for information submitted to national public organisations such as NICE etc, the quality standards in the Code relating to information claims and comparisons had not been applied to the material at issue. Much of Clause 7 applied broadly to all material, including that which was non-promotional rather than being limited to, promotional material as submitted by Genzyme. The Appeal Board noted its rulings above that the material presented and pre-circulated was misleading, inconsistent with the Fabrazyme SPC and disparaging. Genzyme had instigated the meeting. The Appeal Board was extremely concerned that Genzyme's material had focussed on the cost saving via a simple switch to a 0.3mg/kg dose of Fabrazyme without including the clear caveats in its SPC and no mention of important patient safety issues such as adverse events. It was also concerned about the conclusion that the cost savings of switching low dose patients were 'compelling'. The Appeal Board noted that prejudicing patient safety as an example of an activity likely to lead to a breach of Clause 2. The Appeal Board considered that the circumstances brought discredit upon, and reduced confidence in, the pharmaceutical industry and it upheld the Panel's ruling of a breach of Clause 2. The appeal was unsuccessful.

The Appeal Board noted that the LSDEAG was the advisory group for the SCT which in effect could decide on commissioning at a national level. The potential gain to Genzyme in promoting a switch to 0.3mg/kg Fabrazyme was significant. The Appeal Board was so concerned about the content of the material at issue, its potential effects and impression given including the disregard for patient safety, that it decided, in accordance with Paragraph 10.6 of the Constitution and Procedure to require Genzyme to issue a corrective statement to all attendees at the LSDEAG meeting and all recipients of the pre-circulated material if they differed. The published case report should be provided. Details of the proposed content and mode and timing of dissemination of the corrective statement must be provided to the Appeal Board for approval prior to use. [The corrective statement appears at the end of the report]

The Appeal Board also decided that, given all of its concerns above, to require, in accordance with Paragraph 10.4 of the Constitution and Procedure, an audit of Genzyme's procedures in relation to the Code. The audit would take place as soon as possible. On receipt of the audit report and Genzymes's comments upon it, the Appeal Board would consider whether further sanctions were necessary.

Genzyme was audited in February 2015 and upon receipt of the audit report, the Appeal Board was extremely concerned that despite a very critical report which concluded with a number of specific recommendations, Genzyme's comments upon it were exceptionally brief. Indeed the Appeal Board considered that the brevity of the comments demonstrated a lack of engagement. With regard to the audit report, the Appeal Board was deeply concerned that the information which Genzyme had cascaded to its staff about the outcome of Case AUTH/2721/7/14 was not accurate or balanced; this was unacceptable. The Appeal Board considered that there was an apparent lack of insight and leadership with regard to compliance.

The Appeal Board requested, *inter alia*, a more detailed response to the audit report and additionally considered that Genzyme should be re-audited at the end of June 2015; on receipt of the report for that audit it would decide whether further sanctions were necessary.

On receipt of the more detailed response to the audit report from Genzyme whilst the Appeal Board had some concerns, it would await the re-audit report before considering this matter further.

Upon receipt of that audit report in July, together with Genzyme's comments upon it, the Appeal Board noted that although some progress had been made, further improvement was still required. The Appeal Board was concerned that some of Genzyme's anticipated completion dates were long given the action required. Further, Genzyme had not given a completion date for implementation of some of the recommendations.

The Appeal Board was particularly concerned about some training material and considered that Genzyme needed to develop greater in-house expertise. The Appeal Board noted that Genzyme had plans in that regard and aimed to finalise updated materials by 31 August. It was hoped that updated standard operating procedures etc would be finalised by 30 November.

Notwithstanding the provision of certain materials in the meantime, the Appeal Board required that Genzyme be re-audited no later than early December 2015; on receipt of the report for that audit it would decide whether further sanctions were necessary.

Due to major organisational changes Genzyme requested that the re-audit be deferred until February 2016. The Appeal Board was reluctant to do so, given its concerns noted above, but it acknowledged the exceptional circumstances and on receipt of updated material from Genzyme, decided that the re-audit could be deferred until February 2016.

Upon receipt of the report of the audit, together with Genzyme's (now Sanofi Genzyme) comments upon it, the Appeal Board noted that progress had been made since the audit in June 2015; the company had a new general manager and there had been a change in company structure. The audit report highlighted an improvement in company culture although concerns remained about Code training material that must be addressed. On the basis that this work was completed, the progress shown to date was continued and a company-wide commitment to compliance was maintained, the Appeal Board decided that, on balance, no further action was required.

Shire Pharmaceuticals Limited complained about material which Genzyme Therapeutics Ltd pre-circulated and subsequently presented at a meeting of the Lysosomal Storage Disorders Expert Advisory Group (LSDEAG) on 26 February 2014. The material compared Genzyme's medicine, Fabrazyme (agalsidase beta) with Shire's medicine Replagal (agalsidase alfa) both of which were indicated for long-term enzyme replacement therapy in patients with confirmed diagnosis of Fabry Disease.

General comments from Shire

Shire alleged that Genzyme used uncertified, factually incorrect, misleading, inaccurate and promotional information during the LSDEAG meeting. Shire stated that, by Genzyme's own admission, the meeting was instigated by it and was attended by health professionals, patient group representatives and senior NHS managers. Shire attended the meeting on the understanding that it was a non-promotional scientific exchange. Before the meeting, Genzyme pre-circulated a written narrative, 'Genzyme proposal to NHS England for major cost savings in low dose maintenance Fabry patients currently treated with Replagal' and a version of the presentation entitled 'Fabry enzyme replacement therapy: Clarification of the science and the significant cost savings of our tender proposal'. The presentation given at the meeting contained a significant amendment on Slide 4 although this was not notified or clarified for the audience.

Shire stated that Genzyme conceded that it was improper and misleading to have used the word 'biosimilar' at the LSDEAG meeting when comparing Replagal with Fabrazyme and that it would be happy to give an undertaking not to do so in the future. A draft undertaking (which would be inclusive of, but broader than, simply an agreement not to use 'biosimilar') drafted by Shire was rejected by Genzyme. The company stated that its offer was simply to avoid using 'biosimilar' in so far as to avoid any implications that there had been a regulatory review to this effect and that it would consider a communication to this effect to the meeting attendees. Shire stated that the scope of such an undertaking would not address its concerns and in any event, Genzyme failed to provide a draft or explain in what circumstances it would 'consider a communication to the attendees. Shire stated that Genzyme had not made any genuine attempt to resolve the complaint, at any stage, and it considered that inter-company dialogue had been exhausted.

Shire also stated that Genzyme continued to deny that the Code applied – firstly because in its view the LSDEAG was a national public body and was therefore exempt under Clause 1.2 and secondly because the meeting was covered by the Chatham House Rule and so any statements made by Genzyme were not subject to the Code.

Shire noted that Genzyme had created two presentations for the meeting; the initial version was sent in advance to attendees. Information about the revised presentation was only disclosed during the inter-company dialogue. Genzyme had included an additional statement in a second version of the presentation which was used at the meeting. No detail was given to the meeting audience or Shire about the additions and changes made from the version previously circulated; nor was the revised version circulated as a replacement to the group. Genzyme's presentations 1 (pre-circulated) and 2 (used at the meeting) consisted of twenty two slides with the stated aim being to clarify the science for both Fabrazyme and Replagal. Genzyme stated that the presentation would also show the significant cost savings by wholesale switch from Replagal to Fabrazyme.

Shire attended the meeting in response to an unsolicited email request from the chairman of the

LSDEAG. The request was generated in response to a solicited Genzyme meeting held with the chairman in late 2013. Genzyme had noted this within a letter to Shire, dated 27 May 2014, in which Genzyme stated that Shire was responsible for 'unfounded and incorrect rumours' being circulated that the low maintenance dose of Fabrazyme was 'unlicensed' or even 'illegal'. As a result of these rumours Genzyme sought to clarify the situation. Shire strongly refuted this unfounded allegation particularly as a basis for Genzyme's solicitation of the LSDEAG meeting and inappropriate actions during it.

In an email invitation to Shire, the chairman of the LSDEAG stated:

> 'We met Genzyme last week and it took us through the evidence on Replagal and Fabrazyme. I think we will need to return to this at our next EAG meeting scheduled for 2pm on Wed 26 Feb in central London (probably …). Would you be free to attend?
>
> Genzyme's general line of argument will be that the two drugs are equivalent (I don't use that term in any technical sense - just trying to convey the gist) and so if prescribing 0.2mg or 0.3mg of enzyme it would be a lot cheaper to use Fabrazyme.'

Shire understood the LSDEAG meeting was intended to be a non-promotional presentation of the publicly available evidence of both Fabrazyme and Replagal. The stated purpose from Genzyme was that its presentation and narrative would clarify the science and the significant cost savings of its proposal in respect of Fabrazyme. Shire stated that attempting to do this, Genzyme presented misleading and inaccurate information which was inconsistent with the Fabrazyme summary of product characteristics (SPC), promoted actions with the potential to adversely affect patient safety, presented misleading comparisons between Fabrazyme and Replagal, made unsubstantiated claims of superiority over Replagal and promoted Fabrazyme in a setting which was intended to be non-promotional, particularly by presenting cost benefits to switch products, leading to disguised promotion and a failure to certify.

LSDEAG Status

Shire disagreed with Genzyme's view that the LSDEAG was a national public body and therefore material for the meeting was exempt from the Code, pursuant to Clause 1.2.

Shire pointed out that Genzyme repeatedly used NHS England and the Specialised Services Commissioning Function as the supporting evidence that the LSDEAG was a 'national public organisation' but in reality the group was an 'advisory group' which did not have a public constitution or a national public remit. The LSDEAG was thus not, in Shire's view, a '*national public organisation*' in the sense intended by Clause 1.2, particularly as it was not a 'public' organisation in the same manner as that of the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) or the Scottish Medicines Consortium (SMC). Even if it was, it could only be exempt from the Code if the information presented to it was factual, accurate and not misleading; this was not so; Shire alleged that the information presented was not factual, was inaccurate and was misleading and that to present 'cost benefits' at such a meeting was promotional.

The chairman of the LSDEAG, confirmed that the group did not have a formal constitution.

Shire submitted that the LSDEAG provided informal advice to the metabolic disorder clinical reference group (CRG), based on the consensus of patient groups and treating clinicians as members of the LSDEAG. Further, the LSDEAG was not a recognised national public organisation and as such information supplied to it was subject to the Code.

For clarity, Shire noted that the LSDEAG was a sub-group of the metabolic disorders clinical reference groups and as such, it was a group to which the metabolic CRG would turn to for advice about issues related to lysosomal storage disorders.

In terms of governance, anything proposed or recommended by the LSDEAG would need to be supported by the full CRG and only then go through the usual specialised services commissioning route. The LSDEAG was not part of the specialised commissioning function. Genzyme's argument appeared to be that if members of the group also participated in other NHS England groups this was sufficient to make the LSDEAG a national public organisation.

The LSDEAG did not meet any assessment or comparison with the examples of national public organisations given in the Code. Moreover, specialist advisory groups, such as the LSDEAG, were independent bodies which were not therefore part of NHS England but rather asked by NHS England to provide an opinion. The LSDEAG was distinct from the specialised services commissioning function.

Chatham House Rule

Shire noted Genzyme's position that as the meeting was held under the Chatham House Rule, the Code did not apply. Genzyme had stated that it was disingenuous of Shire to complain whilst the meeting was held under this rule and as a result, by raising the complaint Shire would bring discredit to the industry under a Clause 2 breach. Genzyme stated in a call to Shire on 7 May, that if Shire complained to the PMCPA it would inevitably lose and Genzyme would counter claim a Clause 2 breach on that basis.

Shire did not dispute that the meeting was held under this convention or that the intention of the rule was to encourage free discussion by ensuring that comments were not attributable to individuals. Nevertheless, the Chatham House Rule only applied to individuals and not companies. The Genzyme presentations were attributable to Genzyme. In any event, in Shire's view, the existence of this rule did not preclude a complaint and that in trying to use the Chatham House Rule, Genzyme had operated against the spirit of the Code and that the Chatham House

Rule could not be invoked by companies in order to evade the PMCPA's jurisdiction.

In any event, the Chatham House Rule would not protect the Genzyme presentation 1 or its narrative which were pre-circulated before the meeting.

In summary, Shire's view was that the Code applied because the LSDEAG was not a national public organisation but even if it was, the information presented was inaccurate, misleading, not scientifically correct, inconsistent with the SPC and that as the material and activities were promotional Genzyme had breached Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.6, 7.8, 7.9, 7.10, 8, 9.1, 12.1 and 14.1.

Biosimilarity claims

Shire stated that in an inter-company letter, 27 May, Genzyme stated that the term 'biosimilarity' was used for linguistic convenience. The term biosimilar had very specific regulatory meaning and should only be used where comparability studies had been conducted. No such studies had been conducted for Replagal and Fabrazyme. It was unacceptable to use 'biosimilarity' for convenience particularly when the consequences were significant with regard to an unsubstantiated claim.

Shire noted that Genzyme agreed, during a face-to-face meeting, to give an undertaking not to present or suggest, explicitly or implied, that Fabrazyme was biosimilar to Replagal. No such written undertaking had been received by Shire.

Claims that Fabrazyme and Replagal were 'biosimilar' existed throughout the Genzyme presentation (Slides 3, 4, 12, 13, 14 and 21) and the narrative – (page 1, paragraphs 1, 2, 3; page 2, paragraph 3 and page 3, paragraph 5).

Shire alleged that these claims were factually incorrect as Fabrazyme was not authorised as a biosimilar of Replagal. This was a determination that was only valid if made by the European Medicines Agency (EMA). In any event, the EMA's 'Guideline on Similar Biological Medicinal Products' (CHMP/437/04), adopted in October 2005 stated:

> '**Comparability studies** are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorized in the Community' (emphasis added).

Whilst the aforementioned guideline would soon be replaced, the revised guideline contained similar wording on comparability studies:

> 'A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a **comprehensive comparability exercise**' (emphasis added).

The EMA's adopted guideline also stated that the reference medicinal product should contain the same active substance as the biosimilar and the strength should be the same, neither of which was true for Fabrazyme vs Replagal. The guideline stated:

> '[w]hen the pharmaceutical form, the strength or the route of administration is not the same; **additional data in the context of a comparability exercise should be provided**' (emphasis added).

This was acknowledged by Genzyme in its narrative, page 1, paragraph 3.

> '… the products have very different standard doses at 1.0mg/kg for Fabrazyme and 0.2mg/kg for Replagal; this strange situation is not replicated by **any other** biosimilar or generic medicines' [emphasis added].

Inconsistencies with the Summary of Product Characteristics

Shire stated that inconsistencies with the SPC could be found in both Genzyme presentations (Slides 4, 6, 11, 12 and 17) and the narrative (page 1, paragraph 1).

Shire stated that throughout the Genzyme presentation, the company failed to reflect the qualifications in the Fabrazyme SPC as follows:

> 'The recommended dose of Fabrazyme is 1mg/kg body weight administered once every 2 weeks as an intravenous infusion. Alternative dosing regimens have been used in clinical studies. In one of these studies, after an initial dose of 1.0mg/kg of every 2 weeks for 6 months, 0.3mg/kg every 2 weeks maintained clearance of GL-3 **in certain cell types in some patients; however, the long term clinical relevance of these findings has not been established** (see Section 5.1)' (Section 4.2 Posology) (emphasis added).

> 'In the dose finding study, the effects of 0.3, 1.0 and 3.0mg/kg once every 2 weeks and 1.0 and 3.0mg/kg once every 2 days were evaluated. A reduction in GL-3 was observed in kidney, heart, skin and plasma at all doses. Plasma GL-3 was cleared in a dose dependent manner, **but was less consistent at the dose of 0.3mg/kg**. In addition, infusion-associated reactions were dose dependent' (Section 5.1 Pharmacodynamic properties) (emphasis added).

> 'In the post marketing setting, experience was gained in patients who initiated treatment at a dose of 1mg/kg every 2 weeks and subsequently received a reduced dose for an extended period. **In some of these patients, an increase of some of the following symptoms was spontaneously reported: pain, paraesthesia and diarrhoea, as well as cardiac, central nervous system and renal manifestations**. These reported symptoms resemble the natural course of Fabry disease (Section 5.1 Pharmacodynamic properties)' (emphasis added).

In the revised presentation Genzyme added: 'However, the long term clinical relevance of these findings has not been established'.

Shire alleged that Genzyme failed to provide full and complete details with regard to the potential side effects associated with a decreased dosage (ie that there might be a deterioration in the symptoms of Fabry disease) and the fact that the recommended dose was 1mg/kg body weight, all of which were contained in the SPC. Such caveats should have been made, for example, in the conclusions on Slide 22 which stated:

> 'Fabrazyme (0.3mg/kg) provides 50% more protein' and
>
> 'Cost savings of switching low dose patients are compelling'.

[PMCPA note: Slide 22 showed the bar charts (see A3 below). Slide 21 referred to conclusions (See A12 below).]

General comments from Genzyme

Genzyme explained that in 2012 a national tender was held for the provision of treatment for lysosomal storage disorders. Both Genzyme and Shire were awarded a framework agreement to enable participating NHS trusts to acquire Genzyme's and Shire's products for an agreed price. Genzyme submitted two prices for each of the doses mentioned in the Fabrazyme SPC 1mg/kg and 0.3mg/kg. The Specialised Services Commissioning Function (SSCF), part of the Medical Directorate at NHS England consulted with the LSDEAG as part of the tender process. Following the tender there were misunderstandings about Fabrazyme dose 0.3mg/kg (as detailed below) and it was specifically in this context that Genzyme was invited by the SSCF to present at the next regularly scheduled meeting of the LSDEAG (to SSCF at NHS England). The SSCF specifically wanted the LSDEAG to hear the scientific debate between Genzyme and Shire as it had a direct impact on the treatment guidelines (standard operating procedures for treatment) which the SSCF and the LSDEAG had drawn up following the tender.

Genzyme submitted that Shire's concerns arose from an appropriate presentation by a senior Genzyme employee of published science concerning enzyme replacement therapy for Fabry's disease. The presentation was made at the invitation of the SSCF, which was part of the Medical Directorate at NHS England. Genzyme was also asked to send a narrative and presentation including both pre-circulated and presented versions of Slide 4) to NHS England prior to the meeting so that NHS England (not Genzyme as Shire asserted) could pre-circulate these materials to the scientific, clinical and expert representatives of patient associations of the LSDEAG. For this reason, there was no covering letter from Genzyme and the email from NHS England simply stated 'Here are the papers for our meeting on Wednesday. The room is available from 1230 and I will start the meeting at 2pm prompt'.

Genzyme noted that Shire had complained largely about the presentation material designed for the purposes of the invited 15 minute talk, but this must be taken in conjunction with the narrative which was sent as part of the pre-reading materials and referenced during the presentation.

Since the narrative covered important regulatory aspects it was submitted to the MHRA before the meeting; the MHRA made no comment. Genzyme noted that the communications were not written as promotional material, but for the purpose of the invited scientific debate with the expert group. For this reason the materials were not reviewed and certified as promotional material because of the operation of Clause 1.2 as explained in detail below, however the material was reviewed by colleagues including those in medical information to check the facts, NHS structures and referenced material. Genzyme noted that Shire did not review and certify its presentation materials, nor were they formatted as promotional materials which strongly suggested that Shire did not see the meeting as promotional in nature and that Clause 1.2 was relevant.

The Genzyme narrative and presentation were written to clarify confusion about the regulatory status of enzyme replacement therapy doses, to clarify the science supporting Genzyme's 2012 submission requested during the tender process (the submission was also not subject to review because it was not promotional material) and to include all subsequent publications containing comparisons of Fabrazyme vs Replagal. The science had direct implications for doses, regulatory status and cost considerations of fundamental relevance to both the tender process and current commissioning decisions. The relevant extract from the tender document was provided.

Genzyme submitted that the points of fact and science made in the narrative and presentation were:

1 It was very misleading to state that 0.3mg/kg of Fabrazyme was either 'unlicensed' or 'illegal'. Specifically, the regulatory status of the 0.2mg/kg Replagal dose was that it had a conditional licence in Europe with unfulfilled requirements including data on long-term clinical outcomes. This status in Europe was comparable to that of 0.3mg/kg for Fabrazyme which had an SPC caveat 'the long term clinical relevance has not been established'. Whereas long-term clinical data for Fabrazyme 1mg/kg had been submitted and the original conditional licence at 1mg/kg was now a full licence in Europe.

2 The molecules were biologically highly similar on a milligram for milligram basis in a comprehensive range of studies (termed 'biosimilar' or 'biosimilarity' for convenience).

3 The standard doses were 0.2mg/kg for Replagal and 1mg/kg for Fabrazyme.

4 The cost per milligram of Replagal was about four times greater than Fabrazyme in England.

5 The cost per patient at equivalent doses was consequently very different.

Genzyme submitted that before dealing with the allegations of breaches, the full and factual history to the meeting must be clarified for this indicated clearly that Clause 1.2 of the Code was in operation. Clause 1.2 stated 'information supplied

by pharmaceutical companies to national public organisations, such as the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) is exempt from the Code provided the information is factual, accurate and not misleading'. The operation of this clause had been fully discussed with Shire (by telephone, at a face-to-face meeting and in writing on two occasions).

The following account of the history of the meeting and its constitution had been checked and confirmed in an email from a senior representative of NHS England, which had been disclosed to Shire.

Genzyme stated that during the tender process in 2012, it appropriately laid out the very different costs per milligram of the highly similar products Fabrazyme and Replagal, (in fact so similar as to be functionally indistinguishable in any published study on a milligram for milligram basis).

Genzyme stated that in discussions following the tender, during 2012, unfounded and incorrect rumours circulated that the 0.3mg/kg 'low maintenance dose' of Fabrazyme was 'unlicensed' or even 'illegal'. The dose in question was however, fully described in the SPC following submission of data to the regulators as one of the original licence conditions. Unsatisfactory telephone calls and correspondence with Shire did not identify the source of the incorrect allegations nor elicited an agreement that the allegations were inappropriate and incorrect. Unfortunately, these incorrect allegations had continued to obscure the fundamental points that the low maintenance dose of 0.3mg/kg was licensed and that the price per milligram of the two highly similar proteins was more than four-fold different.

During the attempts at clarification Genzyme, was invited by the Advisory Group for National Specialised Services (AGNSS) (as the Specialised Services Commissioning Function was then known) to write an explanatory letter to the (then) AGNSS specialised lysosomal storage disease clinics in January 2013. Despite this letter, the misrepresentations and misperceptions of the regulatory status of the doses of Fabrazyme persisted. The comparative significance of these misrepresentations increased when Replagal's conditional regulatory status in Europe was emphasised by the addition in 2013 of a black triangle warning in the SPC. Furthermore, the application to the Food and Drug Administration (FDA) for a marketing authorization for Replagal had been withdrawn. These misperceptions therefore represented a gross distortion of the actual relative regulatory situations.

Genzyme stated that it had therefore contacted the chairman of the LSDEAG (public health adviser, Specialised Services Commissioning Function at NHS England, previously medical director at AGNSS) in late 2013 to seek advice on how to obtain clarification of the misperceptions arising from the complex regulatory aspects and the underlying science, both peculiar to ultra-rare disease. Subsequently at a meeting between Genzyme and representatives of SSCF at NHS England in January 2014 Genzyme made similar points to those in the presentation about which Shire had complained. The points being that the two proprietary proteins were structurally and functionally very similar, Replagal was approximately four times more expensive per milligram than Fabrazyme and that the 0.2mg/kg dose of Replagal had an outstanding unfulfilled regulatory requirement for long-term clinical data. It was entirely misleading to think of the 0.3mg/kg dose of Fabrazyme as being alone in that respect. These facts had clear relevance to commissioning decisions.

After the meeting in January 2014 Genzyme received the following email from the chairman of the LSDEAG 'I will invite [The named] senior employees of Genzyme and Shire to the 26 Feb meeting of our LSD expert advisory group (2pm in central London). I guess the scientific debate will be most fruitful if we pre circulate the materials'. This confirmed the specific invitation to a debate of the science and its implications for dose and cost convened by the SSCF at NHS England for their LSDEAG and the specific request for written materials.

At the start of the meeting the chairman of the LSDEAG declared the Chatham House Rule to be in operation. Genzyme understood that now the metabolic Clinical Reference Group (CRG) would review the situation. Depending on the outcome of its deliberations, a five stage NHS England process might follow. Genzyme was entirely blind to this very proper and correct process which was in the interests of national commissioning best practice.

Operation of Clause 1.2

Genzyme stated that it had outlined this history in order to show that it had followed an entirely proper interaction with the appropriate national public organisation and during the course of this, received an entirely appropriate invitation to which it responded properly. This was completely relevant to interpretation of Clause 1.2 'information supplied by pharmaceutical companies to national public organisations, such as the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) is exempt from the Code provided the information is factual, accurate and not misleading'.

Genzyme did not accept Shire's interpretation that the LSDEAG was not a national public organisation or Shire's attempts to limit consideration to the LSDEAG while ignoring the central role of SSCF at NHS England in this process and the clear dependent relationship of the LSDEAG to the SSCF.

The meeting at which Genzyme was invited to present was clearly convened by representatives of the SSCF at NHS England. The Health & Social Care Act 2012 imposed a specific statutory duty on NHS England to seek appropriate advice from groups such as the LSDEAG with a broad range of expertise. The meeting was attended by the

chairman of the LSDEAG (public health adviser, specialised services at NHS England) a pharmacy lead, Specialised Services at NHS England, a specialised services commissioning manager at NHS England, a specialised programme of care lead at NHS England), along with the LSDEAG, comprising clinicians and patient association leaders. Genzyme noted that the minutes of the meeting appeared under the NHS England logo. These showed that an appropriate scientific debate took place on the points addressed and that this was simply a regular meeting (the next was pre-scheduled).

The SSCF was manifestly the responsible organisation within NHS England for ultra-rare lysosomal storage disorders and, acting with expert advice from the LSDEAG, advised on treatment and commissioning policies and wrote treatment guidelines, now known as standard operating procedures. To deny the status of the SSCF at NHS England because the LSDEAG had no formal constitution was simply disingenuous. The LSDEAG had given expert advice in specialised commissioning to the NHS for more than seven years, initially within that part of the NHS which was once known as the National Specialist Commissioning Advisory Group (NSCAG). NSCAG transferred to the NHS in April 2007 and then became known as the National Commissioning Group (NCG). The NCG was a Standing Committee of the National Specialised Services Commissioning Group, established as a result of the Carter Review of Commissioning Arrangements for Specialised Services. The NCG then evolved through AGNSS to its current manifestation within the new NHS organisation, NHS England. During these changes the remit of the LSDEAG had continued remarkably unchanged as the advisory group to the NHS commissioning function for specialised services including the treatment of Fabry disease.

Genzyme noted that Shire recently took part in a pilot health technology assessment process with AGNSS which demonstrated its own recognition of it as a body such as those mentioned in Clause 1.2 as stated in its press release on the subject.

Genzyme submitted that given these circumstances and the clear role of the SSCF at NHS England as a national public organisation it was clear that Clause 1.2 of the Code was applicable. Therefore the other provisions of the Code did not apply, other than to require that Genzyme's carefully laid out arguments were factual, balanced and not misleading, as indeed they were. Since these materials were submitted under the provisions of Clause 1.2 they were neither reviewed nor certificated as promotional communications under the provisions of Clause 14, simply because it did not apply. The materials were sent as a direct communication to the chairman at his request who pre-circulated them to the various experts. However it was important to reiterate that although the materials were not certified as promotional material care was still taken to ensure that the material was factual, balanced and not misleading. Finally as discussed above, Genzyme believed that Shire also considered that Clause 1.2 applied to the meeting and this was why it did not certify its own presentation.

Previous PMCPA cases relevant to this case

In respect of the current dispute, Genzyme stated that there was important background in Case AUTH/1299/4/02, TKT-55 v Genzyme. Two extracts of the case report were relevant. The first showed that, in comparing the two products, the Panel agreed that 'structurally very similar' was not an unreasonable description. The second showed that, in 2003, the Panel considered that it was not necessarily correct to extrapolate structural similarity to functional or clinical equivalence as this 'had not been shown' at that time.

> 'The Panel did not agree with TKT-5S's statement that the evidence was clear that in respect of efficacy and tolerability Replagal was materially superior to Fabrazyme. There was no data directly comparing the medicines.
>
> The Panel considered that the nature and extent of the similarities were such that "structurally very similar" was not an unreasonable description; the claim was not misleading or unsubstantiable on this point or inconsistent with the SPC as alleged. No breach of Clauses 3.2, 7.2, 7.3 and 7.4 was ruled.'
>
> 'The Panel noted Genzyme's submission that "functional equivalence was not and should not be construed as a claim of clinical equivalence". In the Panel's view the press release did not make this sufficiently clear. The Panel considered that the claim "functionally equivalent" gave the impression that the *in vitro* data was of direct relevance and significance to the clinical situation and that was not necessarily so. Further, the impression was given that the products were clinically equivalent and this had not been shown. A breach of the Code was ruled.'

Genzyme submitted that since the 2003 case, at least ten separate studies involving comparisons (including one published since the presentation: Weidemann *et al*), had emerged constituting a comprehensive body of confirmatory comparative data, both pre-clinical and clinical. This was presented without omission, in a balanced manner. The publications were, without exception, consistent with not only structural similarity but also functional similarity, clinical pharmacodynamic similarity and clinical similarity. Contrary to Shire's general assertion that Genzyme claimed 'superiority', Genzyme never stated nor implied any practical superiority of the Fabrazyme molecule over Replagal; on the contrary it was specifically stated that they were almost entirely similar. The only differences between the products relevant to the scope of the meeting were their five-fold different doses, four-fold different price per milligram and the precise regulatory status of the various doses. These were the main points of the scientific presentation along with their implications for costs per patient of the products as submitted in the tender in 2012.

Inter-company dialogue

Genzyme stated that it engaged fully in constructive inter-company dialogue with Shire including

rescheduling other commitments during a meeting on 12 May which overran because Genzyme took the inter-company dialogue seriously and it wanted to resolve Shire's concerns. Genzyme supplied full written answers to all of Shire's points which had changed substantially since its original letter dated 28 March. During this dialogue and in light of the minutes of the LSDEAG meeting and Genzyme's wish to be entirely transparent it offered to confirm that its use of the term 'biosimilar' only meant 'biologically highly similar' and did not imply in any way that a regulatory review had taken place, as was clear in the meeting minutes. Finally, it also became apparent during inter-company dialogue that Shire had the pre-circulated version of the presentation and not the version presented at the meeting. A late edit was made to Slide 4 of the presentation, the key difference being the inclusion of the phrase 'the long term clinical relevance has not been established' in the first bullet. This change was made in order to ensure the clearest possible explanation of the regulatory status of each dose. This phrase appeared clearly in the narrative, but was not in the first version of the presentation which was pre-circulated by NHS England during the production of a clear and succinct 15 minute presentation to cover the narrative. This point was also clarified during inter-company dialogue.

Clarification of some assertions as opposed to allegations of breaches

In its complaint Shire attributed various actions and statements to Genzyme which Genzyme submitted required specific context and clarification.

1 Shire stated 'The LSDEAG Meeting was, by Genzyme's own admission, instigated by Genzyme'. The history was clearly explained above and had been explained to Shire. The LSDEAG meeting in question was a regularly scheduled meeting at which Genzyme and Shire were invited to attend the scientific debate by NHS England representatives. One Genzyme employee attended and three employees from Shire attended.

2 Shire stated 'Genzyme pre-circulated a written narrative … a version of the presentation ...'. These were sent by Genzyme to the chairman of the LSDEAG of NHS England who pre-circulated them to the members of the expert advisory group in accordance with his email of invitation 'I guess the scientific debate will be most fruitful if we pre circulate the materials'.

3 Shire stated '[the senior Genzyme employee] conceded that it was improper and misleading … to have used the word "biosimilar" at the LSDEAG meeting ...'.

Whatever Shire thought it might have heard Genzyme explained that the word 'biosimilar' was used for linguistic convenience. This was clearly indicated in the first line of the narrative document 'Without exception, direct comparisons of the molecular properties of the two Fabry enzyme replacement therapies demonstrate milligram for milligram equivalence (biosimilarity)' and in the presentation 'Fabrazyme vs Replagal; very similar molecules – "biosimilar"'. 'Biosimilar' was an appropriate description of the results of all the published comparative data showing equivalence in a comprehensive range of studies without omission or exception, as he went on to demonstrate.

Genzyme offered to write a letter to the attendees to explain that the use of 'biosimilar' was not to imply that regulatory review to this effect had taken place, but was used with a small 'b' as linguistic convenience for 'biologically highly similar in all structural and functional respects'. Genzyme also offered to undertake not to use the term in future in order to avoid Shire's concern that it might give rise to uncertainty about regulatory status. This seemed appropriate as one of Genzyme's overarching objectives in the interactions with NHS England was to clear up regulatory uncertainty about the regulatory status of the doses of Fabry enzyme replacement therapy.

4 Shire stated 'Genzyme continued to deny that the Code applied … because the meeting was covered by the Chatham House Rule …'.

Genzyme submitted that this was a misrepresentation; all statements made by Genzyme's senior employee were subject to the Code. This point was made very clearly during a face-to-face meeting with Shire. Indeed the parties spent a lot of time talking about the Chatham House Rule which Genzyme considered was a red herring. Genzyme stated that it was very clear that the operation of the Chatham House Rule did not mean that any statements made by the company were not subject to the Code and was very surprised therefore that Shire had mentioned this in its complaint. However, as discussed above Genzyme considered that Clause 1.2 of the Code operated and the statements simply needed to be 'factual, accurate and not misleading', which they were. Genzyme was not certain prior to the meeting whether the Chatham House Rule would be in operation or not, but the 'proposal for communication' sent to the chairman of the LSDEAG represented a professional contribution to the scientific debate.

On the other hand, Genzyme knew that it needed to comply with Clause 1.2, which it did. Genzyme's senior employee neither used the background to the meeting itself nor the Chatham House Rule to attempt to communicate any information which was not factual or accurate and did not try to mislead this expert group.

5 Shire stated that information about the revised presentation was only disclosed during the inter-company dialogue. Genzyme submitted that this was not true. In fact a senior employee from Shire and two commercial colleagues were in the meeting and both saw the slide which was presented and heard Genzyme's careful explanation of the regulatory status of both products.

Genzyme submitted that the complaint attempted to make an issue of the edits to Slide 4 and implied that the substitution was somehow deceitful and

deliberate, this was not so. During rehearsal of the presentation, its senior employee found he/she wished to emphasise an important point in respect of the regulatory review of long-term clinical data of both products. The situation being that long-term clinical data had been submitted for 1mg/kg of Fabrazyme, but neither for 0.3mg/kg of Fabrazyme nor for Replagal 0.2mg/kg. The submission of these data for the former fulfilled the specific condition of the original licence for 1mg/kg in direct contrast to Replagal 0.2mg/kg which still had a conditional licence with this outstanding unfulfilled obligation. Slide 4 was edited including insertion of 'the long term clinical relevance has not been established' from the narrative document in order to make this point.

Furthermore, the narrative prominently contained the phrase. There was no omission or deception intended and no deception occurred. The slide was not misleading either in its circulated form or in the way it was presented. It had been edited to ensure complete clarification of the confusion due to circulating rumours about 'unlicensed' and 'illegal' doses.

6 Shire stated 'Genzyme had alleged that Shire was responsible for "unfounded and incorrect rumours" being circulated that the low maintenance dose of Fabrazyme was "unlicensed" or even "illegal"'. Genzyme stated that it had maintained a position of equipoise in respect of the source of these rumours which circulated to the extent that its senior employee was invited to write the letter to the specialist clinics. These rumours had been repeated to Genzyme representatives as questions and statements by physicians and nurses. It was appropriate to seek Shire's view on the matter in order to dispel any doubts over the origin of the rumours. The email exchange was provided and Shire replied as follows:

> 'The code is clear that promotion of medicines must be in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its summary of product characteristics.
>
> I am confident that when discussing the use of a reduced dose of Fabrazyme such as 0.3mg/kg you make reference to the data from the CHMP report that has been added to your SPC. Merely referencing the biomarker data from 2003-2006 that is published in the Lubanda paper from 2009 misses more recent clinically relevant data from that 2010 report in a manner which would not be consistent with clause 7.2 which as you know requires 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**". [Shire's emphasis].

Genzyme noted that Shire's email shed no light on the origin of the rumours and did not contain the same strong denial which was in the complaint 'Shire strongly refutes this unfounded allegation'. Genzyme was pleased that Shire was able to deny any part in the generation of these persistent rumours and the actual source remained a mystery. This denial needed to be considered in the context of the report which Genzyme found on file relating to a meeting on 27 March 2013 with various clinicians and company representatives. This recorded a senior Shire executive as stating that in the opinion of Shire, Fabrazyme 0.3mg/kg was not (a licensed dose).

7 Shire stated that it was 'Genzyme's view that the LSDEAG was a national public body …'. This simply misrepresented the facts, clearly stated above, which was that the SSCF at NHS England was not only a national public organisation, but manifestly the appropriate national public organisation for considering issues related to commissioning of specialised services such as enzyme replacement therapy. The LSDEAG was its advisory group and the meetings were regularly convened for the SSCF to take advice from the group as in this case. Further, if Shire believed that the meeting held on 26 February 2014 was not caught by Clause 1.2, why did it not certify its own materials?

8 Shire stated that 'Genzyme stated in a call to Shire on 7 May, that if Shire complained to the PMCPA it would inevitably lose and Genzyme would counter claim a Clause 2 breach on this basis'. This was not what was said. Genzyme agreed that a call took place concerning Shire's complaint. Shire asserted that Genzyme senior employee's conduct involved multiple Code breaches including Clause 2. The complaints were discussed both in the context of Clause 1.2 and the Chatham House Rule. There was a complete difference of opinion during the call about the interaction of the Chatham House Rule and Clause 1.2 with Shire's complaint; specifically, Genzyme made it clear that making a complaint would disregard the well-known and accepted convention.

9 Shire stated 'that Genzyme agreed, during a face-to-face meeting, to give an undertaking not to present or suggest, explicitly or implied, that Fabrazyme was biosimilar to Replagal'. Shire had misrepresented Genzyme's offer as explained in Point 3 above. Genzyme remained willing to clearly state that the use of the term 'biosimilar' did not imply that any form of regulatory review had taken place, although in Genzyme's view this was made clear during its presentation. Genzyme remained absolutely of the view that the two molecules had been shown to be highly biologically similar in structure and function in a comprehensive range of studies.

10 In the 'Summary' Shire stated 'Genzyme had solicited a meeting with key stakeholders in sensitive commissioning roles within the NHS, the meeting was intended to be non-promotional'. It was true that Genzyme approached the chairman of the LSDEAG in late 2013 to discuss how to clear up the persistent misunderstandings about the 'illegal' or 'unlicensed' status of the 0.3mg/kg dose. Following this, a meeting with other NHS Specialised Commissioning Officers was arranged, but 'solicited' was not an appropriate description of this arrangement. The LSDEAG meeting was a regular scheduled meeting

chaired by the SSCF at NHS England. Genzyme was invited by the chairman of the LSDEAG to attend and make a 15 minute presentation. It was misleading to describe this arrangement as 'solicited a meeting'.

The meeting was arranged by NHS England and was carried out in a proper and transparent fashion. Shire was given the opportunity to attend and counter the arguments put forward by Genzyme. Indeed, Shire took this opportunity and also presented at the meeting. Further, Shire was given the materials which Genzyme were to present before the meeting took place. If Shire considered that Genzyme's presentation was inappropriate promotion, it should have raised its objection then, both with the SSCF and with the PMCPA.

Alleged breaches

Before answering Shire's allegations of breaches on a point-by-point basis, Genzyme stated that its purpose was simply to justify that both the written narrative and the presentation were factual, accurate and not misleading in accordance with the requirements of Clause 1.2. The allegations of breaches of individual clauses, which might be relevant if the piece was a promotional piece, only had relevance in the context of Clause 1.2 insofar as they challenged the factual, accurate and non-misleading nature of the presentation and science.

In respect of all the alleged breaches Genzyme considered that none of them called into question the factual, accurate and non-misleading nature of Genzyme's communications to experts for the purpose of scientific debate and clarification of the tender. In order to avoid repetition this was not stated in respect of each allegation.

The headings below were used for cross-referencing purposes in laying out the justification of the science and its interpretation.

Biosimilarity claims

Genzyme submitted that Shire now raised a semantic argument which obscured the interpretation of the underlying science and the intended meaning and points. It was correct to state that biosimilar had a precise meaning when it was used in a regulatory context and that a claim that a product had been registered as a biosimilar had a very specific regulatory meaning. Conversely, it was usual to call a candidate product a 'biosimilar' prior to regulatory review, which was easily understood. Genzyme submitted it was very careful to explain, when introducing the word, in the narrative, presentation and inter-company dialogue that the term was used in its general sense and not to imply that regulatory review had taken place. Just in case there was any doubt, Genzyme had offered to write a letter to that effect to the participants.

The word 'biosimilarity' was used to indicate that in all emerging published reports of a variety of experimental approaches which comprehensively studied the products, the molecules were found to be biologically highly similar in structure and function. This was carefully laid out in the narrative and presentation. These studies included analyses of structure and chemical composition, assays of receptor binding and cellular internalisation, animal pharmacokinetic and pharmacodynamic studies and clinical studies of both pharmacodynamic and clinical effect, with the caveat that the latter were very difficult in the context of ultra-rare diseases. The successful conduct of a single study of clinical outcome by Genzyme, but not by Shire, illustrative of the unusual difficulties. The adjective 'biosimilar' was a convenient, brief and non-misleading way to state this and would be readily understood by the expert scientific audience. There was no misunderstanding other than by Shire which took it to signify that regulatory review had taken place. Genzyme had been very careful to correct any such misinterpretation in its inter-company dialogue.

The narrative and presentation were very clear in context and did not need to be repeated.

Inconsistencies with the Summary of Product Characteristics

Genzyme denied any inconsistency with the SPC; the necessarily brief communications were suitable for a scientific debate by an expert audience who knew the products very well. The clinicians oversaw the largest Fabry clinics in the world. It would have been inappropriate to have presented the SPC in entirety either in respect of adverse events or warnings or posology.

On the other hand, the narrative gave a succinct and necessarily summarised review of the data available to support the different doses of Fabry enzyme replacement therapy in the SPC of both products. The narrative was explicit about the robustness of data available for the different doses and the patient types who might be suitable for the different doses. Due to the confusion about the regulatory status of 'licensed' and 'illegal' doses the precise details of regulatory review of the products and doses were carefully laid out. Although the clinical experts were familiar with the studies on which the regulatory reviews were based, they might be less familiar with the regulatory processes and the specific intricacies related to ultra-rare diseases such as conditional licences and acceptable burdens of proof.

Genzyme noted Shire's complaint that it failed to reflect qualifications from the SPC, but the phrase 'the long term clinical relevance has not been established', which Shire emphasised, was the very one which was copied from the narrative into the presentation as a late addition. Furthermore, the third phrase about breakthrough symptoms or disease progression which Shire stated Genzyme failed to reflect was covered by 'However, this (low dose) is not appropriate where patients clinically require 1mg/kg of protein, for example when a significant reduction in rate of decline of renal function is required […]or where the higher dose was demonstrated to be necessary for clinical control of breakthrough symptoms as occurred in some patients during the supply shortages'. The experts were very well equipped to judge the scientific merits of this statement for the purpose of the

debate. Quoting long extracts from the SPC would be repetitious and counter-productive in a 15 minute presentation.

In response to a request for further information, Genzyme submitted that the chairman of the LSDEAG initially invited Genzyme in conversation to make a 15 minute presentation at the next scheduled LSDEAG meeting and to supply the accompanying narrative. This was repeated in an email sent 11 February:

'Some practicalities for our meeting on 26 February.

1 The venue, ... will seat 20 people. But we are now a large group, and we have some guests attending. So could I ask people wherever possible NOT to double up on their representation? That said, I don't want to disenfranchise anyone with a key interest.

2 The main item for discussion (60 minutes) is Fabry disease and specifically whether agalsidase alpha and agalsidase beta should be regarded for all practical purposes as interchangeable. I have invited Genzyme and Shire to attend and present for 15 minutes each.

3 The room is booked from 1pm – 4pm. May I ask everyone to get there for 1345 so that we can be set up for a prompt start at 2pm.

4 I will email the agenda and papers round on Monday 24 February. I can't do it earlier because some of the information will not be in the public domain till then.'

The chairman of the LSDEAG then sent an email to Genzyme on 18 February 2014:

> 'Do you think you will be able to send me the presentation for next week's meeting by midnight on Sunday? As a PDF? I'd like to circulate everything on Monday.'

The email chain with Genzyme's senior employee's reply to check whether the narrative should be included were provided. Genzyme checked its recollection with the chairman of the LSDEAG who was in agreement as shown in emails provided by Genzyme.

General comments from the Panel

PANEL RULING

The Panel noted that the meeting at issue took place in February 2014. The 2014 edition of the Code was operative from 1 January 2014. From 1 January 2014 to 30 April 2014 a company would not be ruled in breach because of its failure to comply with newly introduced requirements. The clauses cited by Shire were the same in the previous edition of the Code, the Second 2012 Edition and the current 2014 Code other than Clause 14.1 (Point C below). The change to Clause 14.1 was in relation to who could certify rather than the requirement to certify. Shire referred to the 2014 Code so the Panel used that version bearing in mind that the differences between the two were not relevant to Shire's allegations.

The Director noted that Paragraph 5.3 of the Constitution and Procedure required companies to engage in inter-company dialogue at a senior level and for that dialogue either to be refused or be unsuccessful before a formal complaint to the Authority could be accepted. The Director noted that Paragraph 5.3 referred to successful resolution of inter-company dialogue. It did not refer to the imposition of sanctions during such dialogue. The Director noted that the Authority's published guidance on inter-company dialogue (July 2014) stated, *inter alia*, that 'it is not necessary for a respondent company to admit that an item or activity is in breach of the Code for it to be amended or withdrawn in the course of inter-company dialogue. The success of inter-company dialogue should be judged on whether and to what extent it achieved the action sought and not on why the respondent complied'.

The Director noted that during inter-company dialogue, Genzyme stated that it could undertake not to use 'biosimilar' in future communications to avoid any implication that there had been a regulatory review in this regard and it would consider a communication to this effect to the attendees of the LSDEAG meeting. Shire did not accept that the scope of such an undertaking would address its concerns and stated that Genzyme had not provided a draft or explained in what circumstances it would consider a communication to the attendees. The Director noted that Shire had drafted an undertaking which Shire described as inclusive of, but broader than, simply an agreement not to use 'biosimilar' and this was rejected by Genzyme which nonetheless subsequently maintained its position in relation to an undertaking and 'biosimilar'. Shire stated that Genzyme had not made any genuine attempt to resolve the complaint, at any stage, and it considered that inter-company dialogue had been exhausted.

In the Director's view, and on balance, inter-company dialogue had not been successful. Genzyme's offer in inter-company dialogue was not adequate or sufficiently clear. It stated that Genzyme 'could undertake' not to use the word biosimilar in future correspondence and thus appeared to be conditional. In its submission to the Panel, it appeared that Genzyme wanted to use the term in its general sense. The requirements of Paragraph 5.3 of the Constitution and Procedure had not been met. The Director decided that the complaint about the material which was pre-circulated (the narrative and presentation 1) and subsequently presented (presentation 2) at the LSDEAG meeting on 26 February 2014 should proceed.

The Panel noted that when a meeting, or part thereof, was held under the Chatham House Rule, participants were free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, might be revealed. The Panel noted Genzyme's submission that the application of the Chatham House Rule had been invoked by the chair at the outset of the meeting. It was not within the Panel's remit to comment on such a matter. Its application was a matter for the Chair and meeting attendees. In the Panel's view however, companies could not rely on the Chatham House Rule to circumvent

the requirements of the Code at a meeting where its requirements would otherwise apply. This was acknowledged by Genzyme.

The Panel then went on to consider the nature of the meeting. The audience included clinical experts as well as health professionals from specialised services, including commissioning and patient association representatives. The Panel considered that the audience would be familiar with the products but this did not negate the need to ensure that materials were sufficiently complete, not misleading and fully in line with relevant Code requirements. In this regard, the Panel noted Genzyme's submission that whilst the clinical experts might be familiar with the studies on which the regulatory reviews were based, they might be less familiar with regulatory processes and the specific intricacies related to ultra-rare diseases such as conditional licences and acceptable burdens of proof. The Panel noted both companies' views and Clause 1.2 which stated, *inter alia*, that the term promotion did not include:

- replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them whether of enquiry or comment, including letters published in professional journals, but only if they relate solely to the subject matter of the letter or enquiry, are accurate and do not mislead and are not promotional in nature

  or

- information supplied by pharmaceutical companies to national public organisations, such as the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) is exempt from the Code provided the information is factual, accurate and not misleading.

The Panel first had to consider whether the Genzyme materials could take advantage of either of these exemptions. In this regard, the Panel had to consider how the meeting arose, the parties understanding about its content and the status of LSDEAG.

The Panel noted Genzyme's submission that it had been invited to present scientific evidence at the meeting to address questions and comments regarding the 0.3mg/kg Fabrazyme dose arising following the conclusion of the 2012 tender process. Genzyme noted that SSCF wanted LSDEAG to hear the scientific debate from each company as it had a direct impact on treatment guidelines which SSCF and LSDEAG had drawn up following the tender. The Panel noted that the content of the narrative and presentations appeared to be broader than such matters. As stated by Genzyme, the material covered the differences between the products in relation to dose, price per milligram, the precise regulatory status of various doses and the implications of these points on the cost per patient. The materials provided by Genzyme showed that the meeting organiser made no reference to any cost implications of interchanging products whereas the cost savings were referred to in the narrative title and included throughout. The Panel had no way of knowing what was discussed during telephone conversations and at the meeting which preceded that at issue about the proposed subject matter of the meeting. The Panel considered that, contrary to Genzyme's submission, generally the tender process would be considered promotion of the medicine in question.

In relation to whether the meeting could be considered as a reply made in response to an individual enquiry from members of the health professions, the Panel noted Genzyme's submission. It noted that the LSDEAG meeting organiser initially invited Genzyme to make a 15 minute presentation and repeated the request in an email which stated that 'The main item for discussion (60 minutes) is Fabry disease and specifically whether agalsidase alpha and agalsidase beta should be regarded as interchangeable. I have invited Genzyme and Shire to attend and present for 15 minutes each'. The Panel noted that the sequence of events that led to the meeting in question was initiated by Genzyme which originally contacted the meeting organiser to seek his advice.

The Panel noted that Clause 1.2 defined promotion very broadly as 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. The Panel did not consider that it had been established that the activity amounted to responding to an unsolicited enquiry; the company had initiated the sequence of events and discussion that ultimately led to the meeting. In addition, on the material before the Panel, it appeared that the presentations and narrative might have gone beyond the original ambit of the meeting as evidenced by the email from LSDEAG. In any event, any response to an unsolicited enquiry had to be non-promotional and, in this regard, the Panel noted its comments above about the promotional nature of the tendering process. In the Panel's view, the meeting was inextricably linked to matters arising from the original tender process. In any event, the scope and content of the material and the emphasis on comparative costs was such that it appeared to be promotional. The combined effect of the above points was that, in the Panel's view, Genzyme could not take the benefit of the exemption to the definition of promotion in Clause 1.2 for responses to unsolicited enquiries.

The Panel noted the submissions from both Shire and Genzyme regarding the status of the LSDEAG. The LSDEAG was not given as one of the examples of public bodies in Clause 1.2 which gave, as examples, NICE, AWMSG and SMC all of which had a role in health technology appraisal. The list was not comprehensive. The Panel queried whether the role of LSDEAG when providing advice at the request of the SSCF to NHS England was sufficiently similar to NICE, AWMSG and SMC. The Panel noted that, according to Genzyme, the minutes of the meeting bore the NHS England logo. The position

was unclear. The Panel noted that the exemption in Clause 1.2 only applied if the information provided to the public body was factual, accurate and not misleading. This latter point would need to be considered in relation to the detailed allegations.

The Panel noted that even if the material in question could take the benefit of the exemptions to the definition of promotion as submitted by Genzyme, the material did not fall outside the scope of the Code. It still had to comply with certain aspects of it.

The Panel noted that this was a specialist area. The Panel noted Genzyme's submission that the meeting was attended by clinical experts that were familiar with the studies on which the regulatory reviews were based and were qualified to judge the merits or otherwise of the science presented. The Panel also noted Genzyme's description of those matters on which the experts would not be familiar. The Panel noted that the attendees also included patient association leaders.

The Panel noted that the ABPI had issued documents on biological and biosimilar medicines. One of these documents stated that due to the complex nature, biosimilars required distinct regulatory pathways from those applied to generic medicines. Under European guidelines manufacturers of bisosimilars were required to demonstrate that there were no clinically meaningful differences between the biosimilar and the original biological medicine in terms of quality, safety and efficacy. The Panel was concerned that the first page of the Genzyme narrative stated that 'These very similar proteins fall well within regulatory definitions of biosimilar in all pre-clinical studies' whereas in its response Genzyme submitted that its senior employee was very careful to explain, when introducing the word, in the narrative, presentation and inter-company dialogue that the term was used in its general sense and not to imply that regulatory review had taken place.

The Panel noted that Shire had made detailed allegations regarding presentation 1 and included references to presentation 2 and the narrative.

The Panel noted that the meeting organiser had circulated the narrative and presentation 1 to attendees. Genzyme was aware of this when it provided the materials.

The Panel noted that there appeared to be differences of opinion as to what was said at the meeting. It was impossible to be certain as to what was said and the Panel examined the presentations and narrative in detail.

The Panel noted Genzyme's submission that the scientific presentation was not a comprehensive promotional piece designed to be 'standalone' and the detail was clearly laid out in the narrative. The Panel noted that the presentation and narrative should, nonetheless, be capable of standing alone as regards accuracy etc. In general, claims should not be qualified by the use of footnotes and the like. Although the narrative might have assisted understanding, it was not sufficient to qualify the presentations. The Panel considered that it was difficult to argue that Genzyme was not promoting its product at the meeting.

The Panel's rulings appear at Points A, B and C below.

APPEAL FROM GENZYME

General comments

Genzyme submitted that the object of its appeal was to seek a ruling from the Appeal Board overturning the Panel's rulings that the materials produced by Genzyme for a meeting of the LSDEAG of the Specialised Commissioning Team of NHS England (SCT) were promotional materials and did not fall within the exemption provided in Clause 1.2 of the Code. Genzyme also sought that the Appeal Board overturn the Panel's rulings that the material breached Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.6, 7.8, 8.1, 9.1 and 14.1.

The materials presented to the national public organisation were not promotional (Clause 1.2 exemption)

Genzyme submitted that the conclusions drawn by the Panel in relation to Clauses 3.2, 7.2, 7.3, 7.4, 7.6, 7.8, 8.1 and 14.1 of the Code were a consequence of the Panel's incorrect conclusion that the material was promotional. The material at issue was within the exemption in Clause 1.2 for materials presented to national public organisations and as such could not be considered promotional within the Code. Thus, the clauses mentioned above did not apply.

Genzyme submitted that at the time of the meeting, Shire also considered that materials presented to the meeting were exempt from the requirements of the Code due to the fact that they fell within the scope of Clause 1.2. As discussed below, the materials presented by Shire did not include the black triangle, to indicate that Replagal was under additional monitoring, this signified that Shire did not consider these to be promotional.

Clause 1.1 applied to the provision of promotional material. The material in the present case did not fall within this category since Clause 1.2 provided that certain materials could not be considered to be promotional.

Clause 1.2 stated that information supplied by:

> '…pharmaceutical companies to national public organisations, such as the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) is exempt from the Code provided the information is factual, accurate and not misleading'

Consequently, Genzyme submitted that the requirements imposed by the Code concerning promotional material did not apply to the material produced by Genzyme in response to the specific request of the SCT, a national public organisation (NPO), and distributed by the SCT to the LSDEAG.

The SCT as a National Public Organisation

Genzyme stated that in considering whether the LSDEAG was a national public organisation, the Panel recognised that it was confused over the status of the LSDEAG:

> '…the Panel was unclear whether the LSDEAG was sufficiently similar to the organisations listed'.

As the Panel was evidently unclear about the status of the LSDEAG, Genzyme submitted that it should not have based its findings on an uncertain, and essentially incorrect, assumption that the LSDEAG was not a national public organisation. Moreover, given the fact that the Panel had reservations as to the status and role of the various bodies in this finding, Genzyme submitted that the Panel should not have excluded the exemption to Clause 1.2. Furthermore, the Panel made an error of assessment. It should, in fact, have been considering not, whether the LSDEAG was a national public organisation but rather, whether the SCT was a national public organisation.

Genzyme asked the Appeal Board to consider the exemption in Clause 1.2 in light of the fact that Genzyme provided the material to the SCT and at its request. The SCT shared this information with its advisory body in the same way that NICE shared information with its specialist advisors when making commissioning decisions. In such circumstances, it was essential that the Appeal Board received an authentic account from the chairman of the LSDEAG (from the SCT) who led the process. Genzyme had asked the chairman to attend to confirm that Genzyme presented the material to the SCT following an entirely appropriate invitation from the SCT to present to the LSDEAG in its capacity as advisors to the SCT. This invitation specified what should be in the scope of the material produced by Genzyme for the meeting. Moreover, all the material produced, the presentation and the narrative fell within the scope of the invitation.

Genzyme stated that, unfortunately, the Panel had been misled by the two different accounts of both the role of the SCT in ultra-rare diseases, and of the process led by the SCT prior to the meeting of the LSDEAG. Commissioning in ultra-rare diseases was highly specialised and differed markedly from commissioning arrangements in common diseases.

Genzyme submitted that it appeared that the Panel had been misled by Shire's account. In discussing its findings the Panel repeatedly referred to the LSDEAG, instead of the SCT. The first contact regarding the presentation was between the SCT and Genzyme. There was no contact made by Genzyme with the LSDEAG prior to the meeting. Moreover, the process was conducted under the direction of the SCT. Given the direct relationship between the LSDEAG and the SCT through the LSDEAG's role as an advisory body to the SCT, particularly in relation to the work carried out to develop treatment guidelines, Genzyme submitted that the materials were clearly developed to respond to the SCT's request for further information to clarify various issues following the tender process.

Genzyme submitted that it seemed abundantly clear that NHS England was an NPO. Likewise the SCT, which was the department of the NHS for commissioning specialised services, must be considered an NPO. While it was true that the political and methodological approaches to health technology assessments (HTAs) in ultra-rare diseases remained in flux, until recently the SCT had been entirely analogous to NICE in the context of ultra-rare diseases and therefore within the definition in Clause 1.2 of a national public organisation, such as NICE etc. The fact that the Code used the phrase 'such as' in Clause 1.2 when discussing what constituted a national public organisation led to the legitimate and rational assumption that reference to NICE, AWMSG and SMC in the Code were illustrative examples that were not exhaustive. Other similar bodies might also be recognised as national public organisations.

On its website, NICE described itself as a Non Departmental Public Body (NDPB). The UK Government had produced Guidance on Public Bodies Reform which included the following definition of an NDPB:

> 'A body which has a role in the processes of national government, but is not a government department or part of one, and which accordingly operates to a greater or lesser extent at arm's length from ministers'

The AWMSG described itself as a 'statutory advisory Welsh Assembly-sponsored public body'. The SMC described itself as a 'consortium of stakeholders from Area Drug and Therapeutic Committees (ADTCs) in which representation is derived from ADTCs across NHS Scotland'. Genzyme submitted that it was evident that these three bodies all had quite different constitutions. However they were all examples of bodies exempt from the Code (provided the information given was factual, accurate and not misleading).

Genzyme submitted that the presentation was given at the request of the SCT. The SCT was a function of the Medical Directorate at NHS England. The UK Cabinet Office published an annual data directory of public bodies. The 2013 directory included NHS England as an NDPB. As part of NHS England the SCT indisputably formed part of an NDPB.

Genzyme submitted that the apparent confusion by the Panel between the SCT and its LSDEAG was further demonstrated in the Panel's discussion of the organisations specifically mentioned in Clause 1.2, all of which had a role in health technology appraisals. The implication was that the SCT did not have such a role. This was incorrect. The SCT was the evolution of AGNSS, a development which had, in fact, been evolving during the events which constituted this complaint process.

Genzyme pointed out that its response to the complaint referred to a Shire press release which discussed a HTA conducted by AGNSS in which Shire participated and which was expected to fall within the scope of NICE during 2013. Genzyme acknowledged that responsibility for conduct of HTA

in ultra-rare diseases had recently moved towards NICE bodies during the NHS reorganisations in the last two years. The fact that the professionals who made these assessments had transferred from AGNSS to the SCT confirmed Genzyme's view that the SCT must fall within Clause 1.2. Shire's press release, which accompanied Genzyme's response to the complaint stated:

> 'The AGNSS framework is now in active use in England and will be built upon as part of a robust and transparent process for decision-making by the National Institute for Clinical Excellence (NICE), when it assumes responsibility for the evaluation of ultra-orphan products in April 2013.'

Genzyme submitted that since in the context of ultra-rare diseases, the SCT was, until recently entirely analogous to NICE and remained one of its dependent commissioning structures, the exemption in Clause 1.2 concerning material provided to NPOs applied to material provided to the SCT. This included material supplied for a meeting of its LSDEAG. Information provided to the dependant NICE commissioning bodies must be considered to be analogous to information provided to NICE as these bodies were in fact undertaking part of the role of NICE on the Institute's behalf. It would be erroneous to consider that NICE and its dependant commissioning bodies were not, in many procedural aspects, one and the same. Similarly, the SCT and its dependant expert advisory group, the LSDEAG, must be considered, in many procedural aspects, as one body. As such, information provided to the LSDEAG must be considered to be information provided to the SCT especially as it was provided at the request of the SCT. It was difficult to envisage why there would be one rule for NICE and its dependant bodies and another rule for the SCT and its dependant bodies since both NICE and the SCT were, in many respects, analogous bodies.

Genzyme submitted that Shire press release acknowledged the role in HTA of AGNSS and the SCT. Shire's complaint was a deceptive contrivance. Genzyme had acted in good faith in considering the SCT to be the relevant 'national public organisation'; there was no failure of standards and there was no judgement which risked bringing the industry into disrepute.

Genzyme submitted therefore that material provided to the SCT and LSDEAG in the context of these discussions on the tender process were provided to a national public body within the context of Clause 1.2 of the Code and as such could not be considered as promotional material.

Genzyme submitted that it was interesting to note that, as mentioned above, Shire must have considered that the meeting was exempt from the requirements of the Code under Clause 1.2 because it did not appear to have certified the materials that it presented to the LSDEAG in accordance with Clause 14.1 of the Code. In particular, there was no identifying number and, most importantly, neither the black triangle nor the required standard statements and information concerning the reporting of adverse events were present on Shire's presentation material. This absence strongly suggested that Shire did not see the meeting as a promotional meeting at the time.

Incorrect application of the exemption for unsolicited requests from health professionals

Genzyme submitted that the Panel appeared to have further confused the present issue by considering a second alternative exemption in Clause 1.2 as indicated by the statement:

'The Panel noted its decisions regarding the **two exemptions** to promotion cited by Genzyme.'(emphasis added).

Genzyme submitted that the second exemption referred to by the Panel, concerning replies to unsolicited questions, was never considered or claimed by Genzyme. Nevertheless, the Panel considered this at length, particularly the limitation that such replies fell within provisions of Clause 1.2 '…but only if they relate solely to the subject matter of the letter or enquiry……. and are not promotional in nature'.

The Panel concluded that Genzyme could not claim to rely on the exemption. Genzyme submitted it had never attempted to rely on this particular exemption. Furthermore, Genzyme was concerned that the Panel had imported the proviso from the exemption which Genzyme did not seek to rely on into the exemption that Genzyme did rely on. The Panel therefore, incorrectly concluded that Genzyme could not take the benefit of the exemption for national public organisations. The exemption in Clause 1.2 upon which Genzyme did not seek to rely read as follows:

> '…replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them…'

And contained the proviso:

> '…but only if they relate solely to the subject matter of the letter or enquiry, are accurate and do not mislead **and are not promotional in nature**' (emphasis added).

Genzyme submitted that the exemption which Genzyme relied upon did not contain the proviso that the subject matter was not promotional in nature. This was because the very nature of interactions with national public organisations was that they did not fall under the definition of what constituted promotion for the purposes of the Code even if they might, on occasion, be perceived to be promotional in nature.

Genzyme submitted that it was vital to any consideration concerning the application of an exemption to be clear about the basis for claiming the exemption. It was evident that the Panel was not certain as to the application and scope of either exemption. The Panel's conclusions that Genzyme 'could not take the benefit of the exemption to the definition of promotion' therefore lacked basis along with the consequent inappropriate interpretation of the

individual clauses of the Code, which were intended for promotional material, as also being applicable to submissions to a national public organisation.

Genzyme submitted that there was a very sound underlying reason why the paragraph in Clause 1.2 concerning NPOs, unlike that concerning unsolicited questions, did not include a condition that the material be 'non-promotional'. Unlike the exemption concerning responses to unsolicited enquiries, submissions to commissioning bodies, such as the SCT, clearly concerned efficacy, safety, cost, cost-effectiveness and comparisons of products with other products. This was the basis of HTAs or tender processes which were designed to consider the purchase or sale of a product, including where they were compared to competitor products. Information provided to NPOs might therefore, take account of such considerations and was, encouraged to do so by the NPOs provided that the information was factual, accurate and not misleading. This stipulation concerning factual, accurate and non-misleading information was in fact the only consideration that the PMCPA was empowered to take into account in reviewing the suitability of such materials in light of Genzyme's obligations under the Code. It followed that all the related requirements in the Code concerning promotional material on which the Panel repeatedly relied in its assessment of the presentation and narrative did not apply. The fact that the Panel failed to respect this restriction on its powers of review rendered its decision fundamentally flawed.

Genzyme submitted that in interpreting the factual, actual and non-misleading nature of its presentation and narrative it must be remembered that it was specifically asked to speak to a very small and select group of acknowledged international experts in these ultra-rare diseases and their treatment in the context of a very short presentation in order to facilitate a scientific debate chaired by the SCT. Genzyme specifically designed its communications for this audience and while Genzyme did not wish to air the fact of this complaint and process to all the representatives of the LSDEAG, Genzyme sought the opinion of one leading member, a professor, as to whether Genzyme's use of the term 'biosimilar' was misleading. The professor gave strength to the argument that for this audience and this setting the presentation and the use of the word 'biosimilar' was scientifically accurate, factual and not misleading in accordance with the only relevant requirement of the Code stated in Clause 1.2.

Genzyme submitted that that the inappropriate consideration and confusion by the Panel of the two exemptions in Clause 1.2 had caused misinterpretation. Genzyme never sought an exemption from the application of the Code on the basis of the exemption governing responses to unsolicited enquiries. Genzyme interpreted Clause 1.2 carefully and in good faith. There was no part of Genzyme's interpretation which failed to meet high standards or risked bringing the industry into disrepute. In fact Genzyme went out of its way to be open and transparent by responding to the chairman of the LSDEAG request to share its presentation materials and accompanying narrative in advance of the meeting for circulation to meeting attendees including Shire. Shire did not share its presentation despite the chairman of the LSDEAG's request.

Genzyme acknowledged and agreed with the Panel's assertion that, even if material provided to the SCT fell within the exemption in Clause 1.2, this material must still be factual, accurate and non-misleading. Genzyme submitted that it would refute each of the Panel's findings in each slide.

COMMENTS FROM SHIRE

General comments

Shire fully supported the Panel's rulings.

Shire noted that Genzyme presented to the LSDEAG meeting. The group comprised a professor of biochemistry, consultant physicians (ie health professionals), employees of patient organisations and NHS employees who had a role in commissioning. Shire submitted that this meeting was entirely initiated by Genzyme through an unsolicited request to the LSDEAG chairman.

Shire did not agree with Genzyme that all attendees would be conversant with the regulatory requirements for terms such as 'biosimilar' or treatment options for Fabry disease.

Shire submitted that Genzyme had re-directed its arguments in such a way that this was no longer an appeal of a Panel decision, but an attempt to re-open the preliminary case with alternative arguments and evidence by now inferring that the meeting was with the SCT in place of the LSDEAG. Genzyme's submission was in contravention of the Constitution and Procedure.

Shire noted that exemptions to the Code as described in Clause 1.2, the information provided must still meet the Code standards of being factual, accurate, and not misleading and be capable of substantiation [PMCPA Note: the exemption does not refer to substantiation]. This included information provided to national public organisations such as NICE, SMC and AWMSG as mentioned in Clause 1.2. It was this provision that Genzyme sought to use by claiming that the LSDEAG was a NPO both during inter-company dialogue and in its responses to Shire's complaint. Notwithstanding these arguments and the issues surrounding the status of the LSDEAG, the information presented by Genzyme was required to meet the standards of the Code as above and it failed to do so.

Shire noted the briefing from the chairman of the LSDEAG to Genzyme's senior employee regarding the topics to be discussed: 'The main item for discussion (60 minutes) is Fabry disease and specifically whether agalsidase alpha and agalsidase beta should be regarded, for all practical purposes, as interchangeable.'

However, Shire noted that the subject of the Genzyme presentation as well as the narrative given by Genzyme was:

Presentation 1: 'Fabry enzyme replacement therapy: Clarification of the science and the significant cost savings of our tender proposal.'

Narrative: 'Genzyme Proposal to NHS England for major cost savings in low dose maintenance Fabry patients currently treated with Replagal'.

As a result, Shire submitted that Genzyme had failed to provide the LSDEAG with accurate information and in doing so potentially jeopardised patient safety by providing inaccurate and misleading scientific information. Genzyme's presentation recommended that patients who were maintained on Replagal should be switched to the low dose (0.3mg/kg) of Fabrazyme (eg Cost savings of switching low dose patients are compelling – Genzyme presentation Slide 21).

The Panel concluded that the presentation of data for the low dose (0.3mg/kg) of Fabrazyme was not consistent with the dosage particulars in Section 4.2 or the pharmacodynamics properties in Section 5.1 of the Fabrazyme SPC.

> 'The Panel considered that by failing to mention that the long-term clinical relevance of the reduced maintenance dose of 0.3mg/kg had not been established meant that Slide 4, presentation one was misleading, incapable of substantiation and was not sufficiently complete to enable the recipients to form their own opinion of the therapeutic value of the medicine. The Panel thus ruled breaches of Clauses 7.2, 7.3 and 7.4. In addition, the unqualified statement 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg' on Slide 4, presentation 1 was not consistent with the dosage particulars in Section 4.2 and efficacy details in Section 5.1 of the SPC. The Panel also ruled a breach of Clause 3.2.'

Shire submitted that Genzyme's appeal, sought to exempt the LSDEAG meeting from the Code and in doing so state that the requirements of the Code did not apply and hence the breaches ruled by the Panel did not apply. Furthermore, Genzyme's appeal referred to the LSDEAG meeting as an SCT meeting which was factually incorrect and in itself misleading. The meeting was not an SCT convened or led meeting. It was a meeting of the LSDEAG.

Shire submitted that it is important to note that during inter-company dialogue, one of the areas discussed at length was the validity of the 'LSDEAG' status under Clause 1.2 of the Code. Shire still considered that the LSDEAG meeting remained in scope of Clause 1.2 given that the LSDEAG was not a recognized NPO. Genzyme had now introduced a significant change of direction by referring to the classification of the SCT. It was of note that Genzyme had not provided any details of the hierarchy of these organizations. The LSDEAG had acted as an advisory sub-group for the Metabolic Clinical Reference Group ('CRG'). There was no recognition of the LSDEAG's links with NHS England within the publicly accessible resources of the CRG or NHS England (accessed by Shire 24 April 2014).

Shire submitted that the meeting was convened with and for the LSDEAG, not the SCT. The status of the LSDEAG or indeed the SCT was irrelevant. Under Clause 1.2, regardless of any exemption provided by this clause, the information provided by a pharmaceutical company must be factual, accurate and not misleading. Regardless of status of the group, it was Shire's view that the information provided did not meet the required standards.

Shire referred to the Panel's comment that even if the material in question could take the benefit of the exemption to the definition of promotion as submitted by Genzyme, the material did not fall outside the scope of the Code.

Shire submitted that the Genzyme material, regardless of being an 'LSDEAG' or 'SCT' meeting remained in contravention of the Code principles of being factual, accurate and not misleading as clearly stated by both Shire and the Panel.

Shire submitted that even if the Appeal Board was to conclude that the LSDEAG group was a NPO such as NICE, Genzyme had simply asserted that in this scenario its presentation was factual, accurate and not misleading and had not provided any further arguments in its appeal submission to support its opinion.

On the remainder of the Genzyme submission, Shire submitted there were three main areas where Genzyme's activities were in breach of various clauses these being inconsistencies with the Fabrazyme SPC, biosimilarity claims and cost comparisons. Further details were given below.

APPEAL BOARD RULING

The Appeal Board first decided that as the material at issue included product claims and information on costs it met the broad definition of promotion in Clause 1.2. The Appeal Board noted that the Code also applied to certain non-promotional material and activities. The Appeal Board also noted Genzyme's submission that it did not seek to rely on the exemption to the definition of promotion in relation to replies made in response to unsolicited enquiries. The Appeal Board noted that Genzyme had initiated the process that led to the meeting in question. The Appeal Board noted Genzyme's submission on this matter and thus made no decision on the application of that exemption. The matter for consideration was whether the material could take the benefit of the exemption to the definition of promotion for information supplied to national public organisations such as NICE, AWMSG and SMC which was factual accurate and not misleading. The Appeal Board noted the two elements to the exemption. The Appeal Board noted that the material at issue was provided to the LSDEAG not the SCT. Neither the LSDEAG nor the SCT were included in the examples of public bodies listed at Clause 1.2. The Appeal Board noted that the list was not exhaustive and that other closely similar bodies might be recognised as national public organisations. Nonetheless the Appeal Board considered that the exemption should be narrowly construed. The Appeal Board noted that all three bodies listed had a role in health technology assessment. The chairman of the LSDEAG stated at the appeal that the LSDEAG was established in 2005

to advise him/her in his role and provide medical input to commissioning. The decisions of the bodies listed in Clause 1.2 were publicly available and yet it noted from the representatives of Genzyme at the appeal that the minutes of the LSDEAG could only be publicly sourced via a freedom of information request. The Appeal Board considered that the LSDEAG/SCT were fundamentally different to those bodies listed in Clause 1.2. The Appeal Board noted that unlike the organisations listed in Clause 1.2 the SCT had commissioning powers. The procurement role of the SCT was an important consideration as was the fact that the meeting was at Genzyme's request as part of the tender process. The Appeal Board considered all the circumstances and decided that the SCT/LSDEAG was not sufficiently similar to the examples cited in the relevant exemption and thus could not take the benefit of that part of the exemption for national public bodies such as NICE, AWMSG and SMC. The Appeal Board noted that the exemption under Clause 1.2 did not apply and it now needed to consider the appeal of the Panel's detailed rulings.

The Appeal Board noted Genzyme's submission that the LSDEAG was an expert audience. The Appeal Board noted the membership included non medical members including patient organisations.

A Genzyme Presentations 1 and 2

1 Slide 3 headed 'Fabrazyme vs Replagal; very similar molecules – "biosimilar"'

The slide stated 'Identical gene and amino acid sequences – EPAR (European published [sic] assessment report)'.

COMPLAINT

Shire noted that Slide 3 stated that both Replagal and Fabrazyme 'consist of 398 amino acids' and that they had 'identical sites of glycosylation'. These data were presented out of context and firstly neglected to advise the audience of the different methods of production; and secondly failed to provide a complete picture of the information presented in the two scientific discussions (European Public Assessment Report (EPARs) Replagal and Fabrazyme - EMEA 2004) which were not designed to be used as a comparison. Shire alleged that these data were unable to support the claim of biosimilarity which was in breach of Clauses 7.2, 7.3 and 7.4.

In addition, Shire made general allegations about biosimilarity and Slide 3 as part of its general comments above.

RESPONSE

Genzyme stated that it was uncertain what Shire meant by 'out of context'. It was true that there were two methods of production; this was well known by the expert audience. The 'humanised properties' sometimes claimed to be attributable to Shire's immortalised human fibrosarcoma based method had been the subject of considerable debate. However, this scientific debate simply addressed published data concerning attributes which had been measured, as opposed to conjectured, and which showed, without published exception, the molecules were biologically structurally and functionally highly similar ('biosimilar').

The extracts from the EPARs were intended to simply show that the gene and amino acid sequences and glycosylation sites were the same, consistent with 'biosimilarity' although obviously only one component of the comprehensive range of data which were published and were presented in a factual, balanced and non-misleading way. Genzyme saw no relevance in the observation 'not designed to be used as a comparison' with regard to these simple statements of scientific fact.

PANEL RULING

The Panel considered that the term biosimilar would be taken in the regulatory sense rather than Genzyme's submission that it was used in the general sense. The narrative stated 'Without exception, direct comparisons of the molecular properties of the two Fabry enzyme replacement therapies (ERT) demonstrate milligram for milligram equivalence (biosimilarity)', 'These very similar proteins fall well within regulatory definitions of biosimilar in all pre-clinical studies' and 'Despite the biosimilarity, the products have very different standard doses at 1.0mg/kg for Fabrazyme and 0.2mg/kg for Replagal; this strange situation is not replicated by any other biosimilar or generic medicines'.

The Panel noted its comments above with regard to the EMEA requirements for authorization of biosimilar medicines; studies needed to be carried out to show that the medicine was similar to the reference medicine and did not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy. No such studies for Fabrazyme and Replagal had been performed and it was thus misleading and inaccurate to use the term 'biosimilar' when comparing the two medicines; it could not be substantiated.

The Panel noted its general comments above. The Panel noted its decision that Slide 3 was misleading and inaccurate and considered that this meant that presentation 1 and presentation 2 and the narrative could not take the benefit of the exemption to the definition of promotion in Clause 1.2 as set out in the Panel's general comments above for information supplied to national public organisations such as NICE, AWMSG and SMC both as the Panel was unclear whether the LSDEAG was sufficiently similar to the organisations listed and secondly, the material did not meet the criteria listed ie that it was factual, accurate and not misleading. The Panel noted its general comments on the promotional nature of the tender process and materials above. The Panel noted its decisions regarding the two exemptions to promotion cited by Genzyme. In the Panel's view, the material was thus promotional and had to comply with the relevant requirements of the Code.

With regard to Slide 3, the Panel ruled a breach of Clauses 7.2 and 7.3 as the use of the term 'biosimilar' was misleading and thus the comparison was misleading. The Panel noted that in its general comments Shire referred to the use of 'biosimilar'

in Slides 3, 4, 12, 13, 14 and 21 and the Genzyme narrative. The Panel considered that its ruling on this point also applied to Slides 4 (Point A2), 21 (Point A12) and the narrative (Point B) where the allegation was only referred to in Shire's general comments. In addition, the Panel noted that Shire had made specific allegations in relation to Slides 12, 13 and 14 and these were considered below (Points A7 and A8).

The Panel did not consider that the lack of information regarding the different methods of production and a complete picture of the information presented in the two products' EPARs was misleading as alleged. In the Panel's view, the health professionals would not be misled into prescribing a product which Genzyme claimed to have identical gene and amino acid sequences and sites of glycosylation as the competitor to which it was compared. The EPARs were not designed to be used as a comparison but this did not necessarily prevent comparing features of the information in the EPARs. The Panel ruled no breach of Clause 7.2 and 7.3 in this regard. The Panel noted that whilst the three statements on Slide 3 were not misleading, they did not substantiate the claim of biosimilarity in the heading of the slide as alleged. A breach of Clause 7.4 was ruled.

APPEAL FROM GENZYME

Genzyme submitted that the Panel had incorrectly placed too much weight on Shire's assertions about the use of the word biosimilar to support the contention that the material was misleading.

Genzyme submitted that the Panel had made several references to the '…specific regulatory meaning…' of the term 'biosimilar'. As an example Shire alleged that 'The term biosimilar had very specific regulatory meaning and should only be used where comparability studies had been conducted'. Furthermore, 'The Panel considered that the term biosimilar would be taken in the regulatory sense rather than Genzyme's submission that it was used in the general sense'.

Genzyme submitted that medicinal products in the European Union ('EU') were governed by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use. The Community Code did not define the term 'biosimilar', nor did the word 'biosimilar' appear anywhere in the Community Code. Furthermore, 'biosimilar' molecules were not subject to a specific marketing authorization process in the EU. In claiming that the term 'biosimilar' had a very specific regulatory meaning Shire sought to appropriate this term for exclusive use within the marketing authorization procedure provided in Article 10.4 of the Community Code. This was both misleading and incorrect. Article 10.4 defined a biosimilar as:

> '…a biological medicinal product which is similar to a reference biological product [BUT] does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences related to raw materials or differences in manufacturing processes of the biological medicinal and the reference medicinal product'.

Genzyme submitted that the term 'biosimilar' was complex and the definition rather less precise than that of a generic medicinal product. This was well known by all concerned in industry and regulation who continually struggled with this issue. Even if Article 10.4 defined products considered to be 'biosimilars' it was evident that the definition related to a particular category of product not to a regulatory authorization procedure. Furthermore Fabrazyme met the definition in Article 10.4. It was a biological medicinal product which was similar to Replagal (the reference biological product in this case) but it had an entirely different manufacturing process.

Genzyme submitted that the definition could not be interpreted as meaning that only medicinal products in relation to which an application has been made for marketing authorization might be permitted to fall within the meaning of 'biosimilar'. Moreover, in light of the fact that all medicinal products authorised in the EU, whether classified as innovative, generic or biosimilar, followed the same route to marketing authorization, the claim made by Shire, that the term biosimilar had a 'very specific regulatory meaning' was evidently misleading and incorrect.

As acknowledged in the Panel's rulings, Genzyme used the term 'biosimilar' as a convenient, brief and non-misleading way of indicating that all emerging published reports of a variety of experimental approaches which comprehensively studied the products, found the molecules to be biologically highly similar in structure and function. Genzyme explicitly stated that the term was being used for ease of language. It was difficult to see how the words 'ease of language' could be mistaken to mean 'specific regulatory meaning'. Furthermore, the audience were highly trained experts in this area very familiar with the universal use of the term 'biosimilar'. This was demonstrated in the letter from the professor, a member of the LSDEAG which stated 'As a whole, the data you presented make a compelling case for the two molecules being equivalent in terms of their pharmacological properties and clinical potency; that they are 'biosimilar' in their biological properties.' The use of the term was not misleading. In addition, Genzyme had submitted the narrative to the Medicines and Healthcare Products Regulatory Agency (MHRA) highlighting the regulatory aspects in advance of the meeting and the MHRA made no comment. It might validly be anticipated that the MHRA would have commented if there had been related issues.

Genzyme submitted that as there was no 'very specific regulatory meaning' of the term 'biosimilar', it was difficult to see what legal basis or rationale the Panel used to conclude that the term biosimilar should be considered in the regulatory sense. In the absence of a specific regulatory meaning, the term biosimilar must be considered within the bounds of the ordinary meaning of the word. This was the explicit intention of Genzyme, as stated during the presentation and at the outset of the narrative document and this was recorded in the minutes of the meeting.

Genzyme submitted that this was particularly important as the Panel used the incorrect conclusion that the word 'biosimilar' had a very specific regulatory meaning to conclude that the presentation was misleading and therefore Genzyme could not rely on the exemption in Clause 1.2.

COMMENTS FROM SHIRE

Shire alleged that consistent use of claims related to mg/mg biosimilarity which as explained below added no substance to the requirements to substantiate such claims and therefore remained in breach of the Code as they were inaccurate, misleading and not factual.

Shire alleged that the claim 'Fabrazyme vs Replagal; very similar molecules – 'biosimilar" could not be substantiated as there was no formal head to head study.

APPEAL BOARD RULING

The Appeal Board noted the heading to Slide 3 and its content. The Appeal Board considered that the term 'biosimilar' would be taken in the regulatory sense rather than the general sense. There was insufficient clarity in Slide 3. The Appeal Board noted Genzyme's submission that it had never intended 'biosimilar' to refer to the regulatory meaning and in hindsight it would have used a different term to reflect a more general definition. In this regard the Appeal Board noted that Genzyme had not used the term 'biosimilar' in those extracts of the tender document provided. It noted Genzyme's submission that pharmacodynamic data had been published after the tender document had been submitted and before the meeting took place. The Appeal Board noted Shire's submission that there was no formal study comparing Replagal and Fabrayzme nor were they biosimilar in the regulatory sense. The Appeal Board considered that in relation to the term 'biosimilar' the use of 'biosimilar' on Slide 3 was misleading and hence the comparison was misleading and incapable of substantiation. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4. The appeal was unsuccessful. The Panel's rulings of a breach of Clauses 7.2 and 7.3 also applied to Slides 4, 21 and the Genzyme narrative and thus the Appeal Board's ruling also applied to this material. The appeal was unsuccessful.

2 Slide 4 headed 'Biosimilar, but very different licences; SmPC wording'

Presentation 1, Slide 4, stated that the 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose 0.3mg/kg' and that the Replagal standard dose was 0.2mg/kg. The slide also stated that Fabrayzme had a 'full European licence' with a Phase IV study showing a reduction of clinical events, 'Replagal provisional license [sic] unfulfilled obligations 1a, b, c and 2a'. It included a black triangle and monitoring statement. The slide ended with 'US application unsuccessful again'.

Presentation 2 Slide 4 was similar. It included beneath 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg' a statement that 'the long term clinical relevance has not been established'. In addition, the reference to unfulfilled provisional licence obligations also stated 'no prospective study of long term clinical outcome, *inter alia*,' [sic]. The slide ended with 'US licence application unsuccessful again 2012'.

COMPLAINT

Shire noted that Genzyme's two presentations showed different statements and Genzyme only focused on the presentation used at the meeting in its inter-company response of 27 May. Genzyme confirmed that presentation 1 was received by all the delegates. The revised version which was presented on the day (presentation 2) was not circulated as a replacement to presentation 1 and no disclosures were made about the amendment. In presentation 1, the sentence 'the long term clinical relevance has not been established' was omitted from Slide 4.

Shire alleged that the statement of 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg' was not consistent with the Fabrazyme SPC.

Shire noted that the Genzyme slide stated under the print screen of the Replagal SPC that the 'US licence application unsuccessful again'. This comment related to Shire withdrawing the US licence application on 14 March 2012. These comments were irrelevant to the UK market but were in any event misleading and disparaging as they inferred that the FDA had Replagal withdrawn after multiple attempts by using the word '…again'.

Shire alleged breaches of Clauses 3.2, 7.2, 7.3, 7.4 and 8.

RESPONSE

Genzyme submitted that Slide 4 was edited as the presentation was rehearsed soon before the meeting to provide prompts to ensure that the regulatory situation was clearly explained without omission even though it was clearly laid out in detail in the accompanying narrative. When the Genzyme employee talked to these slides the context and the difference between the doses and the data which supported these doses were fully explained. The scientific presentation was not a comprehensive promotional piece designed to 'standalone'. It was not produced as such, nor reviewed as such and was not subject to the provisions of the Code other than Clause 1.2.

Genzyme submitted that the statement 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg' appropriately summarised the actual SPC wording in the context of a 15 minute presentation to experts for the purposes of scientific debate. The actual SPC wording was:

'Posology
The recommended dose of Fabrazyme is 1mg/kg

body weight administered once every 2 weeks as an intravenous infusion.

Alternative dosing regimens have been used in clinical studies. In one of these studies, after an initial dose of 1.0mg/kg every 2 weeks for 6 months, 0.3mg/kg every 2 weeks may maintain clearance of GL-3 in certain cell types in some patients; however, the long term clinical relevance of these findings has not been established (see section 5.1).'

Genzyme stated that nature of Shire's complaint about the US licence application was unclear with respect to the use of the word 'again'. It was a matter of fact that in addition to the withdrawal on 14 March 2012, there was a previous Replagal Biologic Licence Application which resulted on 14 January 2003 in an unsuccessful hearing at the Endocrinologic and Metabolic Drugs Advisory Committee Meeting to the FDA. Subsequently the licence application was withdrawn by TKT (TKT was acquired by Shire in 2005). The use of the word 'again' could not be construed as either misleading or disparaging, it was factually and grammatically correct and it would have been extraneous to go into further detail of the two separate applications.

PANEL RULING

The Panel noted Shire's allegation that 'the long term clinical relevance has not been established' in relation to the reduced maintenance dose of Fabrazyme (0.3mg/kg) was omitted from Slide 4 in presentation 1 which was received by all of the delegates. The revised version which was presented on the day (presentation 2) contained the above phrase, however, it was not circulated as a replacement to presentation 1 and no disclosures were made on the day about the amendment.

The Panel noted the SPC wording:

'Posology

The recommended dose of Fabrazyme is 1mg/kg body weight administered once every 2 weeks as an intravenous infusion.

Alternative dosing regimens have been used in clinical studies. In one of these studies, after an initial dose of 1mg/kg every 2 weeks for 6 months, 0.3mg/kg every 2 weeks may maintain clearance of GL-3 in certain cell types in some patients; however, the long term clinical relevance of these findings has not been established (see section 5.1).'

The Panel noted that the narrative gave more detail about the differences between the dosing of the products and the original licences which Genzyme stated were granted in exceptional circumstances for both products. The licences included specific obligations to conduct and submit data on long-term clinical outcomes. According to Genzyme, these had been fulfilled with Fabrazyme 1mg/kg but not Replagal 0.2mg/kg. Genzyme stated in the narrative that the caveat in respect of Fabrazyme 0.3mg/kg simply mirrored the continued provisional licence status of Replagal 0.2mg/kg 'in the absence of clinical outcome data approved as sufficient by the regulators'. Fabrazyme's full European licence following fulfilment of all the original specific obligations including submission of Phase IV data showing reduction of the rate of clinical events which Genzyme stated validated the efficacy of 1mg/kg. The narrative stated that in contrast the failure to meet the specific obligations for Replagal led to the EMA announcement on 25 April that the product was included on the list of products requiring additional monitoring and the need for a black triangle. The Panel noted that Shire's allegation related to the slides not the narrative.

The Panel considered that by failing to mention that the long-term clinical relevance of the reduced maintenance dose of 0.3mg/kg had not been established meant that Slide 4, presentation one was misleading, incapable of substantiation and was not sufficiently complete to enable the recipients to form their own opinion of the therapeutic value of the medicine. The Panel thus ruled breaches of Clauses 7.2, 7.3 and 7.4. In addition, the unqualified statement 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg' on Slide 4, presentation 1 was not consistent with the dosage particulars in Section 4.2 and efficacy details at Section 5.1 of the SPC. The Panel also ruled a breach of Clause 3.2.

With regard to the prominent statement 'US licence application unsuccessful again'. The Panel noted with concern that Slide 4 in the pre-circulated slides, presentation 1, provided by Shire, which was the subject of complaint, differed, to that provided by Genzyme. Shire's Slide 4 finished 'US license application unsuccessful again', Genzyme's version included the year 2012 in both presentation 1 and 2. It was unclear why the versions differed. The Panel noted Shire's submission that the comment related to Shire withdrawing the US licence application on 14 March 2012. The Panel noted Genzyme's submission that there was a previous Replagal Biologic Licence Application which resulted on 14 January 2003 in an unsuccessful hearing at the Endocrinologic and Metabolic Drugs Advisory Committee Meeting to the FDA. The narrative explained that Shire withdrew the Biologics License Application on 14 March 2012. In the Panel's view, the statement implied that the FDA had rejected the Replagal application again which was misleading and inaccurate. The Panel ruled a breach of Clause 7.2. The Panel also ruled a breach of Clause 8.1 as it considered that the implication was disparaging. These rulings applied to presentations 1 and 2.

During its consideration of this case the Panel was concerned that the discussion regarding 0.3mg/kg did not make it clear that this was used after an initial dose of 1mg/kg for 6 months. The statement regarding use of the dose in one study was also not included. The full context was missing. It requested that Genzyme was advised of its views.

APPEAL BY GENZYME

Genzyme submitted that in light of its general comment above, that the material provided to the

SCT fell within the exemption in Clause 1.2 and was not promotional, none of the requirements in Clause 7 of the Code applied to Slide 4. This was simply because such requirements applied to promotional material only. Clause 7 did not expressly state that non-promotional material was excluded from the requirements. However, read in tandem with the provisions of Clause 1.2 concerning information provided to NPOs this clause could only be interpreted as meaning that the requirements for which it provided applied only to promotional material. Phrases included in Clause 7 such as '…a comparison is only permitted in promotional material if…'; '…when promotional material refers to published studies, clear references must be given…' supported Genzyme's understanding of the scope of Clause 7. As such, Genzyme denied breaches of Clauses 7.2, 7.3 and 7.4 as they did not apply to Slide 4.

Moreover, Clause 3.2 expressly governed '…the promotion of a medicine…' and stated:

> '…the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics.'

Genzyme submitted that this clause thus did not extend to material that was not promotional such as the material in Slide 4 presented to the SCT, an NPO. As such, there were no grounds for a ruling by the Panel on the basis of Clause 3.2.

Despite the assertion that Clause 3.2 did not apply, Genzyme submitted that it took great care to appropriately present the potential use of 0.3mg/kg and referred to it in the context of 'reduced maintenance dose', or 'low dose maintenance (patients)' in the presentation. The narrative specifically stated in the second sentence that '… patients who are currently stable on low dose ERT…' were those who might be considered for treatment with low dose Fabrazyme. The expert clinical audience would readily recognise these patients were clinically similar to those who had been stabilised after 6 months' treatment with 1mg/kg as described in the SPC. Indeed a large proportion of patients taking Replagal in the UK were treated with Fabrazyme 1mg/kg prior to the supply shortage. The clinicians in the audience would readily recognise such patients and contextualise them against the limited clinical evidence base available in an ultra-rare disease. The meaning did not deviate from the SPC and did not mislead as evidenced by the letter from a member of LSDEAG. It was intended to stimulate a clear scientific debate as proposed by the SCT.

Genzyme submitted that since the presentation given at the meeting included the qualification that 'the long term clinical relevance has not been established', neither Shire nor the Panel could argue that the information on the slide was misleading. Statements could not be perceived as misleading as the claim was qualified on the day of the meeting itself when the presentation was made. Provided the experts at the meeting were aware of the qualifying statement when the information was presented, as they were, an assertion that the information was misleading could not be upheld. Moreover, the members of the LSDEAG present at the meeting would all know that the Fabrazyme SPC contained similar statements. The failure to replicate such statements in the materials provided before the meeting, which were provided in good faith and in haste in response to a request from the SCT, could not be considered to be misleading once the statements were inserted in the actual presentation.

Genzyme submitted that it did not intend that its statement 'US licence application unsuccessful again' should imply that the FDA withdrew Shire's applications. The statement was introduced within the context of a slide which specifically discussed the authorizations and regulatory status for both products. Indeed the title of Slide 4 was 'Biosimilar, but very different licences; SPC wording'. The status of the various licence applications in the US were relevant in the context of such discussions. The statement did not expressly state that the FDA withdrew the applications. Rather, it constituted a simple statement of fact; two applications for Replagal were withdrawn. Genzyme underlined that the company did not intend to infer that the FDA rejected both applications. Genzyme had used this statement in good faith. It was, therefore, incorrect to allege that the company disparaged Shire in this statement.

Genzyme submitted that its employee wished to clarify the precise relative regulatory status of both products and the results of the actual reviews by regulatory authorities of the clinical data. Statements about the FDA made in the context of a 15 minute presentation were not disparaging but simply corrected the misleading perceptions of the comparability of the two products which were propagated by Shire. It was simply not possible to cover the complex details of the history of the two unsuccessful Replagal applications in the US in a 15 minute presentation; BioCentury had devoted many pages of an article to this matter alone. In this regard, the email from Shire's product specialist (described below and provided) included the sentence 'Interestingly, the wording within the US prescribing information has never included data or reference to 0.3mg/kg dosing'. Shire introduced the consideration of FDA review; Genzyme simply tried to correctly contextualise this. Genzyme's actions could not be judged to be bringing discredit on the industry as it was simply presenting the facts appropriately in order to correct misperceptions deliberately caused by Shire.

COMMENTS FROM SHIRE

Shire noted Genzyme's failure to mention that the long-term clinical relevance of the reduced maintenance dose of Fabrazyme 0.3mg/kg had not been established and its inclusion of an unqualified statement 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg'. Inconsistent claims were outside of the current European licence thus rendered these elements out of label and in breach of the Code by being inaccurate, misleading and not factual or capable of substantiation.

APPEAL BOARD RULING

The Appeal Board noted the Fabrazyme SPC wording:

> 'Posology
>
> The recommended dose of Fabrazyme is 1mg/kg body weight administered once every 2 weeks as an intravenous infusion.
>
> Alternative dosing regimens have been used in clinical studies. In one of these studies, after an initial dose of 1.0mg/kg every 2 weeks for 6 months, 0.3mg/kg every 2 weeks may maintain clearance of GL-3 in certain cell types in some patients; however, the long term clinical relevance of these findings has not been established (see section 5.1).'

The Appeal Board noted that 'the long term clinical relevance has not been established' in relation to the reduced maintenance dose of Fabrazyme (0.3mg/kg) was omitted from Slide 4 of the pre-circulated presentation (presentation 1); the revised presentation used on the day (presentation 2) included the phrase. It was not circulated as a replacement to the pre-circulated presentation and no disclosures were made on the day about the amendment.

The Appeal Board considered that by failing to mention that the long-term clinical relevance of the reduced dose of 0.3mg/kg had not been established, Slide 4 of the pre-circulated presentation was misleading, incapable of substantiation and was not sufficiently complete to enable the recipients to form their own opinion of the therapeutic value of the medicine. The Appeal Board thus upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4. In addition, the unqualified statement 'Fabrazyme standard dose 1.0mg/kg or reduced maintenance dose of 0.3mg/kg' on Slide 4 of the pre-circulated presentation was not consistent with the dosage particulars in Section 4.2 and efficacy details at Section 5.1 of the SPC. The Appeal Board also upheld the Panel's ruling of a breach of Clause 3.2. The appeal was unsuccessful.

The Appeal Board noted the statement in the pre-circulated presentation provided by Shire 'US licence application unsuccessful again'. Slide 4 in presentations 1 and 2 provided by Genzyme stated 'US application unsuccessful again 2012'. It was unclear why the versions differed. The Appeal Board noted that Shire had withdrawn its US licence application. The Appeal Board considered that the statement implied that the FDA had rejected the Replagal application again and this was misleading and inaccurate. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The Appeal Board also upheld the Panel's ruling of a breach of Clause 8.1 as it considered that the implication was disparaging. These rulings applied to the pre-circulated presentation and the presentation used at the meeting. The appeal was unsuccessful.

3 Slide 6 headed 'ERT annual cost per 70kg patient at different doses' and Slide 22 headed 'ERT annual cost per 70kg patient at licensed doses'

The slides were similar; the headings were different. Each included a bar chart with one column showing the selling price of Fabrazyme 1mg/kg, another for Fabrazyme 0.3mg/kg and a third for Replagal. The bar charts for Fabrazyme 0.3mg/kg and Replagal were bracketed together and described as 'low dose maintenance'. They showed a significant saving in favour of Fabrazyme 0.3mg/kg. The Replagal bar also showed an assumed tender price.

COMPLAINT

Shire noted that on Slides 6 and 22 Genzyme compared the prices of Fabrazyme 1mg/kg, Replagal 0.2mg/kg to Fabrazyme 0.3mg/kg and alleged that this was not consistent with the Fabrazyme SPC as detailed above. A breach of Clauses 3.2 and 7.2 was alleged.

RESPONSE

Genzyme disagreed that the doses were not consistent with the SPC and referred to its comments above.

PANEL RULING

The Panel considered that the SPC for Fabrazyme was clear that the recommended dose was 1mg/kg body weight. The reference to the use of alternative dosing regimens in clinical studies was in relation to one of these studies when after an initial dose of 1mg/kg every two weeks for 6 months, a dose of 0.3mg/kg every two weeks might maintain clearance of GL-3 in certain cell types in some patients. The Panel further noted the SPC statement that the long-term clinical relevance of these findings had not been established. The Panel noted its comments above at Point A2 about the 0.3mg/kg dose.

The Panel noted that the Replagal SPC stated that it was administered at a dose of 0.2mg/kg body weight. No other dose was mentioned in the posology section of the Replagal SPC. The Panel considered that the impression from the slides was that Replagal and Fabrazyme at 0.3mg/kg had similar status according to the respective SPCs and this was not so. Insufficient information about the status of the 0.3mg/kg dose had been given. The Panel considered that the depiction of the 0.3mg/kg dose was inaccurate given the detail in the Fabrazyme SPC. The impression given was misleading and inconsistent with the SPC. The Panel ruled a breach of Clauses 7.2 and 3.2.

APPEAL BY GENZYME

Genzyme repeated its view (Slide 4 above) that, as the material provided to the SCT was not promotional, the requirements imposed by Clauses 7.2 and 3.2 did not apply to Slide 6. Neither the Panel nor Shire had alleged that the information in Slide 6 was not factual, accurate and non-misleading [sic].

COMMENTS FROM SHIRE

Shire stated that Genzyme's use of cost comparisons based upon incorrect assumptions led to a non-promotional meeting becoming promotional in an attempt to influence the audience

to switch products based upon an unqualified dose and biosimilarity claims. Examples of these were Slide 6 and 22. The comparison of the prices of Fabrazyme (1mg/kg and 0.3mg/kg) with Replagal (0.2mg/kg) was inaccurate, misleading and inconsistent with the Fabrazyme SPC.

APPEAL BOARD RULING

The Appeal Board considered that the SPC for Fabrazyme was clear that the recommended dose was 1mg/kg body weight and the Replagal SPC stated that it was administered at a dose of 0.2mg/kg body weight. The reference in the Fabrazyme SPC to the use of alternative dosing regimens in clinical studies was in relation to one study when after an initial dose of 1mg/kg every two weeks for 6 months, a dose of 0.3mg/kg every two weeks might maintain clearance of GL-3 in certain cell types in some patients. The Appeal Board further noted the SPC statement that the long-term clinical relevance of these findings had not been established. None of this was clear in Slides 6 and 22.

The Appeal Board considered that the slides implied that Replagal 0.2mg/kg and Fabrazyme at 0.3mg/kg had similar status according to the respective SPCs and this was not so. The slides also implied that the two cited doses were clinically equivalent maintenance doses. The Appeal Board noted that over the year not all patients would stay on the maintenance dose. The Appeal Board considered that insufficient information about the status of the Fabrazyme 0.3mg/kg dose had been given and that the slides were extremely poor in that regard. The Appeal Board considered that the depiction of the 0.3mg/kg dose in the bar charts was inaccurate given the detail in the Fabrazyme SPC. The impression given was misleading and inconsistent with the SPC. The Appeal Board upheld the Panel's ruling of a breach of Clauses 7.2 and 3.2. The appeal was unsuccessful.

4 Slide 7 headed 'Sakuraba *et al*: Minimal differences in glycosylation except M6P – the ligand'

The slide reproduced table 1 from Sakuraba *et al* (2006) which compared the monosaccharide analysis from that study and Lee *et al* (2003). Data for mannose-6-phosphate (M6P) for Replagal and Fabrazyme were circled.

COMPLAINT

Shire noted that Sakuraba *et al* was referenced with no additional background to the type and purpose of the study eg that it was *in vitro*. A table taken directly from the publication was modified and only one set of values that differed between the two products were highlighted. Shire alleged that Genzyme had 'cherry-picked' the data for mannose-6-phosphate neglecting to highlight the different values of galactose, fucose and *N*-acetylglucosamine and therefore was not in line with the findings of both studies cited on this slide. Sakuraba *et al* was not specifically about glycosylation and should not be used independently to substantiate the claims on the slide. No study limitations or caveats were mentioned.

Shire alleged breaches of Clauses 7.2, 7.3, 7.4 and 7.8.

RESPONSE

Genzyme submitted that Sakuraba *et al* was well known to the clinical experts in the audience and the findings were similar to Marchesan *et al* (2012) quoted in the narrative and presentation. An international expert on receptor binding and cellular trafficking to the lysosome, was an author of Marchesan *et al* and had been invited to the meeting by the chairman to present results, but the expert considered there was no need for the presentation as the scientific facts were clear and undisputed.

In respect of the accusations of 'cherry-picking', mannose-6-phosphate was the specific ligand which enabled cellular internalisation, it might be the sugar moiety with the greatest known functional importance and its density per molecule was therefore of potential significance. That was why it was highlighted – as opposed to 'cherry-picked'. The slightly higher density of M6P in Fabrazyme might be a theoretical advantage and might be consistent with the slightly increased receptor binding and cellular internalisation observed for Fabrazyme, but no significance was attached by Genzyme to these possible differences. The point made (repeatedly) was that, without published exception, Replagal had not been shown to hold any molecular advantage that might predict a five-fold difference in dose and, on a milligram for milligram basis, the proteins were biologically highly similar.

Further, in respect of 'cherry-picking', the other sugars in the glycan structures did not have determined functional significance other than as linkers, with the possible exception of fucose which appeared to replace mannose-6-phosphate in the glycan structures (to the extent that it is possible to determine these things) and the density was consequently higher in Replagal than Fabrazyme; however this was not relevant to the scientific debate and outside the scope of a 15 minute presentation. It was simply inappropriate to call the focus on the functional ligand 'cherry-picking'. These data were selected as they were consistent with all the other published data indicating biosimilarity.

Genzyme knew that the presence of one of the author's in the expert group would be sufficient if there were any serious questions about the molecular aspects as presented, which there were not.

PANEL RULING

The Panel noted Shire's allegation that Sakuraba *et al* was referenced with no additional background about the type and purpose of the study. The slide did not state that the study was *in vitro* but the Panel considered, however, that the audience would be clear that the data derived from *in vitro* testing.

The Panel noted that the table was taken directly from the publication. The only modification by Genzyme was that the data for mannose-6-phosphate was

circled as Genzyme submitted this was the specific ligand which enabled cellular internalisation. Values for galactose, fucose, mannose, N-acetylglucosamine and sialic acid although not circled were included. The Panel did not consider that Genzyme had 'cherry-picked' data as alleged. The purpose of Sakuraba *et al* was to compare the effects of agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme) on cultured human Fabry fibroblasts and Fabry mice. M6P residue content was listed as a parameter to be compared. Sakuraba *et al* stated that successful targeting of the α-galactosidase in Fabry disease was strongly dependent on the presence of M6P residues on the sugar chains of the enzyme preparations. The enzyme activity increases in cultured fibroblasts, kidneys, heart and spleen were higher for Fabrazyme than Replagal and this might have resulted from differences in M6P residue content in the sugar chains of the two preparations. The Panel queried Genzyme's submission that no significance was attached by it to those possible differences: there appeared to be no other reason for highlighting and comparing the M6P results. Indeed, such differences were mentioned in the narrative which made the theoretical basis of the discussion clear. The Panel had no way of knowing precisely how the slide was presented. The slide had to be capable of standing alone. The Panel did not consider the slide misleading due to the highlighting of the M6P data. It appeared that Genzyme had a cogent reason for selecting that outcome. No breach of Clauses 7.2 and 7.3 were ruled. The Panel noted that no study limitations or caveats related to the table were given on the slide but did not consider that this necessarily rendered the table misleading as alleged. Shire bore the burden of proof and in the Panel's view Shire had not established that the study caveats etc should have been included on the slide. The Panel ruled no breach of Clauses 7.2, 7.3 and 7.8. The Panel thus considered that the table was capable of substantiation and ruled no breach of Clause 7.4.

5 Slide 8 headed 'Lee *et al*: Replagal is not more potent'
Slide 9 headed 'Sakuruba [sic] (2006): Any potency differences favoured Fabrazyme'

Slide 8 showed graphs of resonance units against protein concentration and mean response against activity for both products with regard to M6P binding and fibroblast update.

Slide 9 compared enzyme activities and M6P content for both products and stated that there was no difference in stability in plasma. Animal results favoured Fabrazyme.

COMPLAINT

Shire noted that the supplementary information to Clause 7.2 stated that 'claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be linked with some practical advantage, for example, reduction in adverse reactions or cost of effective dosage'.

Shire submitted that Genzyme appeared to link the potency claims with a claim of greater cost effectiveness. However, the cost effectiveness claim was itself misleading, meaning that the use of potency claims could not be justified.

Shire noted that Lee *et al* (2003) was cited with no additional background information on study design and type. Only two graphs were presented and missed vital context in order to fully interpret the data. Additionally, the study was not powered to compare potency and the data shown was the measured protein concentration and enzyme activity. Contrary to Slide 7, the results showed no difference in enzyme activity between Replagal and Fabrazyme which had not been appropriately presented. The study did not substantiate the claim of potency and was therefore not clinically relevant and was misleading. No study limitations or caveats were mentioned.

Slide 9 was designed to highlight potency differences in the products but described only limited information about the study. The presentation did not mention that not all animal tests were completed with Replagal due to the limited quantity available to test and therefore did not substantiate the claim that 'animal results favoured [Fabrazyme]'.

Shire alleged that these results were 'cherry-picked' and Genzyme had omitted data showing the additional differences between the two products. Presenting these data without qualifications was misleading and unbalanced. Shire alleged that with regard to 'cherry picking' results and claiming that 'Replagal is not more potent' and 'Any potency differences favoured Fabrazyme' the presentation was in breach of Clauses 7.2, 7.3, 7.4, 7.8 and 12.

RESPONSE

Genzyme stated that it was not clear why Shire proposed that Genzyme had linked 'claims of potency' to greater cost effectiveness. Genzyme did not make any claims for superior potency, it only sought to show that there was no measurable difference in potency which might account for a five-fold difference in dose and that on a milligram for milligram basis the proteins were biologically equivalent. The prices per patient were simply calculated by multiplying the actual doses of Fabry enzyme replacement therapy used, body weight and the very different costs per milligram of the two products.

The results were only 'cherry-picked' insofar as they were relevant to assessing biosimilarity in the context of a scientific debate and could be fitted into the time available. It would clearly not be possible to present all results from all the published studies in a 15 minute presentation. As stated before the clinical experts were very well qualified to judge the merits or otherwise of the science presented and there was no debate on these points.

PANEL RULING

The Panel noted that neither Slide 8 nor 9 contained any reference to cost or cost effectiveness. It thus failed to understand Shire's allegation in this regard. Slide 6 of the presentation showed annual costs but did not mention cost effectiveness. Shire might have been attempting to make a general point that the statements regarding potency and the similarity

between the products reinforced Genzyme's data regarding the cost comparison of Fabrazyme 0.3mg/kg with 0.2mg/kg Replagal. However, there was no such link on the slides. The Panel did not know precisely how the slides were presented at the meeting. The narrative discussed potency in relation to the products' similarity, not their cost-effectiveness. The Panel ruled no breach of Clauses 7.2 and 7.3 with regard to Shire's allegations about cost effectiveness claims in relation to Slides 8 and 9.

The supplementary information to Clause 7.2 stated that care should be taken with the use of *in vitro* data and the like so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

Lee *et al* was a biochemical and pharmacological comparison of certain features and concluded that the GL-3 clearance data in conjunction with the biochemical analysis supported structural and functional equivalence of the two proteins and that this suggested that the different dosing regimens were as a result of the different clinical trial designs rather than a functional difference between the two proteins.

The Panel considered that the two slides were not designed to evaluate potency *per se*. Slide 8 did not claim superior potency only that Replagal was not more potent. Slide 9 stated that if there were any potency differences these favoured Fabrazyme. The Panel noted that the final bullet point on Slide 9 stated that 'animal results favoured [Fabrazyme]'. The Panel queried whether it was sufficiently clear that Slides 8 and 9 related to *in vitro* data and the clinical effects of Fabrazyme and Replagal were not being compared. There was no clinical data to substantiate a claim that Fabrazyme was more potent than Replagal. The Panel considered that the slides were misleading in this regard. A breach of Clauses 7.2, 7.3 and 7.4 was ruled. The Panel ruled a breach of Clause 7.8 as the graphs on Slide 8 were not presented in such a way as to give a clear, fair, balanced view of the matters with which they dealt. No breach of Clause 7.8 was ruled with regard to Slide 9 as there was no artwork on that slide.

The Panel noted its general comments and its finding at Point A1 above that the presentations and narrative were promotional. The Panel did not consider that they would be seen as anything other than promotional. Thus, the Panel did not consider that either Slide 8 or Slide 9 constituted disguised promotion and ruled no breach of Clause 12.1.

APPEAL BY GENZYME

Genzyme repeated its view that the requirements in Clauses 7.2, 7.3, 7.4, and 7.8 did not apply to the information in Slides 8 and 9 to the extent that these requirements concerned promotional materials. As such, there were no grounds for a ruling by the Panel on the basis of any of these clauses.

Genzyme submitted that it had not made any claims for superior potency. Both Sakuraba *et al* and Lee *et al* were well known to the clinical experts at the SCT, including LSDEAG. As the Panel accepted in its previous ruling concerning Slide 7, given the audience present at the LSDEAG it was sufficiently clear that the data related to *in vitro* studies. Furthermore, there were no statements in either Sakuraba *et al* or Lee *et al* that would support the contention that Fabrazyme was more potent than Replagal. Genzyme noted the Panel's acknowledgement in relation to Slides 7 and 11 that the audience would already be aware of this study and article. As such, Genzyme submitted that the scientific information presented in these slides was well known within the expert community present at the LSDEAG meeting. The information contained no statements that Fabrazyme was more potent than Replagal and as such, was not misleading. A breach of Clauses 7.2, 7.3, 7.4 and 7.8 should not, therefore, have been concluded by the Panel.

COMMENTS FROM SHIRE

Shire provided no specific comments on Slides 8 and 9.

APPEAL BOARD RULING

The Appeal Board noted that Slide 8 was headed 'Lee at al: Replagal is not more potent'. Lee *et al* was an *in vitro* biochemical and pharmacological comparison yet there was no explanation in the slide that this was so. The Appeal Board noted that Slide 9 was headed 'Sakuruba [sic] (2006): Any potency differences favoured Fabrazyme'. The Appeal Board noted that the final bullet point on Slide 9 stated that 'animal results favoured [Fabrazyme]'. The Appeal Board queried whether it was sufficiently clear that Slides 8 and 9 compared *in vitro* data for Fabrazyme and Replagal, not their clinical effects. There was no clinical data to substantiate the impression from Slides 8 and 9 that Fabrazyme was more potent than Replagal. The Appeal Board upheld the Panel's ruling of a breach of Clauses 7.2, 7.3 and 7.4. The Appeal Board also upheld the Panel's ruling of a breach of Clause 7.8 as the graphs on Slide 8 did not give a clear, fair, balanced view of the matters with which they dealt. The appeal was unsuccessful.

6 Slide 11 headed 'Vedder *et al* (2007): The only attempted comparison of 0.2mg/kg vs 0.2mg/kg'

The slide included a graph comparing Fabrazyme 0.2mg/kg, Fabrazyme 1mg/kg and Replagal 0.2mg/kg in relation to decrease of LysoGb3 activity and month of treatment. It also included the quote 'Although the number of patients is small, it is unlikely that large differences in clinical potency exist at equal dose' and referred to a follow up publication, van Breemen *et al* (2011).

COMPLAINT

Shire stated that Vedder *et al* was a small head-to-head study and included an off-label dose of Fabrazyme 0.2mg/kg. Within the overall context of the two Genzyme presentations which were designed to lead the audience to the conclusion that the products were equivalent, Shire alleged breaches of Clauses 3.2, 7.2 and 7.3.

RESPONSE

Genzyme stated that while it was true that 0.2mg/kg of Fabrazyme was not in the label, from a scientific viewpoint a comparison of two products at the same dose was not only perfectly valid, but, indeed, the preferred approach for comparing potency. In this case, the results were consistent with equivalence of the two products both in respect of clinical effect (in the initial publication) and in respect of the pharmacodynamic marker LysoGb3 measured in stored samples and published three years later by van Breemen *et al*. It would have been inappropriate to omit this comparative study from this scientific debate and the expert clinicians were well placed to judge the implications of both the small numbers and the associated caveats, which were intrinsic to attempts to conduct studies in ultra-rare diseases.

PANEL RULING

The Panel noted its previous general comments about the nature of the audience and disease and the promotional nature of the activity.

It considered that the data presented in this slide was inconsistent with the SPC due to the reference to the 0.2mg/kg Fabrazyme dose. The slide did not mention the number of patients (34 in Vedder *et al* and 43 in van Breemen *et al*). The graph was from van Breemen *et al* and the quotation was from Vedder *et al* referred to in the slide heading.

The Panel considered that it was likely that the audience would be aware of this data. It accepted that it might be interesting from a scientific view point but considered as it used an unlicensed dose of Fabrazyme it was misleading and inconsistent with the SPC. Thus the Panel ruled breaches of Clauses 7.2, 7.3 and 3.2 of the Code.

APPEAL BY GENZYME

Genzyme repeated its view that since the material provided to the SCT was not promotional, Clause 7.2, 7.3 and Clause 3.2 did not apply to the information in Slide 11 to the extent that the requirements concerned promotional material. Consequently, there were no grounds for a ruling by the Panel concerning the content of this slide on the basis of Clause 3.2, 7.2 and 7.3. Genzyme referred to the Panel's conclusion that the information presented would be interesting from a scientific view and it was likely that the audience would be aware of this data.

COMMENTS FROM SHIRE

Shire noted that the Fabrazyme 0.2mg/kg dose referred to in Slide 11 was not mentioned in the Fabrazyme SPC. The Panel had ruled a breach of Clause 7.2, 7.3 and 3.2 for being misleading and inconsistent with the Fabrazyme SPC

APPEAL BOARD RULING

The Appeal Board agreed with the Panel's view that the reference in the slide to a 0.2mg/kg Fabrazyme dose was inconsistent with the SPC. The slide did not state the number of patients (34 in Vedder *et al* and 43 in van Breemen *et al*). The graph was from van Breemen *et al* and the quotation was from Vedder *et al* cited in the slide heading.

The Appeal Board noted that Panel's comments that it was likely that the expert audience would be aware of this data but considered that as the slide referred to an unlicensed dose of Fabrazyme it was misleading and inconsistent with the SPC. Thus the Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2, 7.3 and 3.2 of the Code. The appeal was unsuccessful.

7 Slide 12 headed 'Smid *et al* (2011) supply shortage'
Slide 13 headed 'Switch study after recent FDA Replagal withdrawal'

Slide 12 featured a graph which referred to changing Fabrazyme 1mg/kg to Replagal 0.2mg/kg fortnightly or Fabrazyme 0.5mg/kg monthly in relation to LysoGb3. Beside the graph was the statement 'Consistent with biosimilarity and equivalent pharmacodynamic dose response'.

Slide 13 referred to 15 male patients switched from Replagal 0.2mg/kg to Fabrazyme 1mg/kg in whom LysoGb3 decreased by 39.5% p=0.0002. It also included 'An increased pharmacodynamic response with an increased dose of biosimilar ERT' [Enzyme Replacement Therapy]. The slide was referenced to Barranger *et al* (2014).

COMPLAINT

Shire noted that neither Smid *et al* (2011) nor Barranger *et al* (2014 unpublished) were designed to compare the products to indicate biosimilarity or equivalent pharmacodynamic dose response and were therefore used in a misleading manner.

Slide 12 included the statement: 'Consistent with biosimilarity and equivalent pharmacodynamic dose response'.

Slide 13 included the statement: 'An increased pharmacodynamic response with an increased dose of biosimilar ERT'.

The doses used in Smid *et al* showed patients switching from Fabrazyme 1mg/kg every other week to either Replagal 0.2mg/kg fortnightly or Fabrazyme 0.5mg/kg every other week or 0.5mg/kg monthly which were inconsistent with the product licence.

The graph on Slide 12 was not clear and the results shown were only for male patients, consisting of half the patient population at the start and Genzyme did not provide any study detail or balanced safety information.

Both slides showed switching studies that were conducted during the Fabrazyme global product shortage. The full detail of potential risk of switching patients to a lower dose of Fabrazyme was not made explicit in the presentation with regard to adverse events. The European Medicines Agency Assessment Report (EMEA/H/C/000370, 9 July 2010), on the

consequences of the Fabrazyme shortage concluded that as more patients were prescribed lower doses of Fabrazyme, more adverse events were reported, and subsequently patients were moved to Replagal or to 1mg/kg of Fabrazyme. The following statement from the report showed that patients might not be maintained on the lower Fabrazyme dose:

> 'There is a clear trend of increasing reports of (serious) AEs since the shortage. **The higher the percentage of patients receiving the lowered dose, the higher the number of AEs [adverse events] reported**. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage decreased, as well the absolute number of reports. A subgroup of patients seems to be doing well on the lower Fabrazyme dose' (emphasis added).

Shire noted that the heading of Slide 13 included '… after recent FDA Replagal withdrawal'; this comment related to Shire withdrawing the US licence application on 14 March 2012. However, these comments were misleading and disparaging to Shire by inferring that the FDA had Replagal withdrawn. It was, in fact, Shire's decision to withdraw the application.

Shire alleged that the information presented in Slides 12 and 13 was disparaging, misleading, unbalanced and inconsistent with the Fabrazyme SPC in breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.8 and 8.

RESPONSE

Genzyme stated that Shire's assertion that these studies were not designed to compare the products to indicate biosimilarity or equivalent pharmacodynamic dose response and were therefore used in a misleading manner was manifestly incorrect and misleading.

a) Barranger *et al* set out to compare Replagal at 0.2mg/kg with Fabrazyme at 1mg/kg when US patients were forced to change from the Replagal IND study after the Replagal licence application withdrawal. Barranger *et al* 'Evaluation of glycosphingolipid clearance in patients with Fabry disease treated with agalsidase alfa who switched to agalsidase beta' stated 'The INFORM study was designed to determine if a decrease in plasma lyso-GL-3 can be seen in patients who were switched from 0.2mg/kg of agalsidase alfa every 2 weeks to 1.0mg/kg of agalsidase beta every 2 weeks'. This clearly described a prospective crossover comparison of the two products using a pharmacodynamic marker. The study was adequately powered as was shown by the p value of 0.0002 for Lyso-GL-3 (lysoGb3, see below) at the end of the 6 month treatment period.

b) Smid *et al* set out to report observed changes during the supply shortage when dosage reductions were forced. The conclusion in the abstract read 'No increase in clinical event incidence was found in the adult Dutch Fabry cohort during the agalsidase beta shortage. Increases in lysoGb3, however, suggest recurrence of disease activity'. The study report showed that the 'agalsidase beta shortage' meant either a product switch or a dose reduction and that the pharmacodynamic marker lysoGb3 was used to compare this to baseline treatment with Fabrazyme 1mg/kg. While the study was not adequately powered, and therefore not adequately designed to detect a difference in clinical event rate, it was adequate to detect the equivalent statistically significant increases in lyso-Gb3 which occurred on either product switch or dose reduction of Fabrazyme to an equivalent dose to that of Replagal.

Globotriaosylceramide (Gb3) was the main substrate which accumulated in Fabry disease; both Gb3 and its more water soluble and chemically reactive metabolite globotriaosylsphingosine (lyso-Gb3) had been measured in plasma and tissue and used in clinical studies of Fabry disease as pharmacodynamic markers. It was incorrect to state that the studies were not designed to compare the products as this was the specific purpose. In both cases lyso-Gb3 performed as a remarkably stable pharmacodynamic marker and clearly demonstrated an equivalent response at equivalent doses.

The male patients alone were shown as there were only 3 females in the study, not 'half the patient population' as stated by Shire. Furthermore, as was well known by the experts in the audience, Fabry disease was an X-linked disease and the female form was milder than the male form so that the few females in Smid *et al* had low lyso-Gb3 levels, well within the normal range and were therefore not amenable to study. Thus Genzyme did not include those results in the 15 minute presentation, which could not possibly cover all data from all publications mentioned. The experts in the audience were familiar with the studies.

The presented lyso-Gb3 data from Smid *et al*, Barranger *et al* and van Breemen *et al* were intended to demonstrate that the dose dependent clinical pharmacodynamic effect of Fabry enzyme replacement therapy irrespective of brand was seen consistently in all the published studies. The clinical experts were well qualified to judge the validity or otherwise of this.

Shire stated that Genzyme was not explicit about the potential risk of switching patients to a lower dose of Fabrazyme and, in this respect, quoted the report from the European Medicines Agency (EMA) about adverse event reports during the supply shortage, this was discussed during the meeting.

Firstly, the purpose of the presentation was not to examine the merits of switching to lower doses of Fabry enzyme replacement therapy, but to examine the evidence which might support a switch of brands in patients who were already established and stable on low dose maintenance treatment. This was made very clear in communications from Genzyme 'However, this (low dose) is not appropriate where patients clinically require 1mg/kg of protein, for example when a significant reduction in rate of decline of renal function is required or

where the higher dose was demonstrated to be necessary for clinical control of breakthrough symptoms as occurred in some patients during the supply shortages'.

Genzyme submitted that Shire's arguments were also based on the observation of increased frequency of adverse events observed during the prolonged supply shortage when many patients who had received 1mg/kg Fabrazyme either had their doses reduced on Fabrazyme or their enzyme replacement therapy protein dose reduced by switching to Replagal 0.2mg/kg. This required examination as was explained by the Genzyme employee at the meeting.

In the UK, at the onset of the supply shortages there were teleconferences in which all clinics participated. In respect of Fabry disease, the patients on 1mg/kg Fabrazyme were 'triaged' into those who must stay on that dose if at all possible, those who would move to reduced doses of Fabrazyme between 0.3 and 0.5mg/kg and those who could switch to Replagal. Triage was based on both objective and subjective clinical assessments. It was inevitable that there would be a 'nocebo' (opposite of placebo) effect in a forced dose reduction in addition to the symptoms seen in about 25% of patients in the Lubanda study after dose reduction to 0.3mg/kg. It was thus not surprising that there was an increase in reporting of possible 'breakthrough' disease manifestations in this uncontrolled, unblinded and enforced dose reduction. The clinicians who managed the dose reductions during the supply difficulties were all present and did not disagree with this analysis.

Genzyme submitted that all reports of symptoms or other evidence of disease progression should be interpreted in the context that Fabry disease was a progressive disease and symptoms and disease progression occurred regardless of the dose used as demonstrated in the Lancet figure 4 (Slide 16) or Banikazemi (clinical event rates vs placebo (Slide 15)).

Genzyme noted Shire's claim that the reference to the withdrawal of the application was disparaging; Shire relied on a rather particular interpretation of the brief headline to support this claim. It was not possible to go into detail about the reasons for withdrawal and not appropriate other than to state that a 9 page article was published entitled 'The Replagal Saga' on 25 June 2012. In producing the short headline to a slide in a short presentation Genzyme would have preferred to use 'BLA' (Biologic License Application), but thought that this acronym would not be as readily meaningful to the clinical experts. The accompanying narrative stated it in full 'on March 14th 2012 Shire withdrew the Biologics License Application (marketing authorization application) two weeks prior to the scheduled FDA advisory committee meeting'. There was no attempt to mislead, disparage or present anything other than facts.

PANEL RULING

The Panel noted that Slide 12 presented data following either changes in the dose of Fabrazyme or a switch to Replagal. These changes were a result of a supply shortage of Fabrazyme which according to Smid *et al* was due to viral contamination at Genzyme's production facility in June 2009 which led to a world-wide shortage and led to involuntary dose reductions or switch to Replagal. Slide 13 referred to the withdrawal of Replagal by Shire from the FDA approval process.

The Panel noted its previous comments and rulings about the use of the term 'biosimilar (Panel's general comments and Point A1) and considered that they were relevant to Slides 12 and 13. Slide 12 featured the phrase 'Consistent with biosimilarity …' and Slide 13 referred to 'an increased dose of biosimilar ERT'. The Panel considered that Slides 12 and 13 were misleading in this regard for the reasons set out at Point A1 and ruled breaches of Clauses 7.2 and 7.3. The material did not substantiate the claim for biosimilarity and a breach of Clause 7.4 was ruled.

The Panel noted that the doses illustrated on Slide 12 were inconsistent with the Fabrazyme SPC and noted its comments on the 0.3mg/kg Fabrazyme dose at Point A2 above. Smid *et al* referred to EMA advice on 25 June 2009 that 'priority should be given to children, adolescent, and adult male patients. However, adult female patients in whom the disease is less severe may receive Fabrazyme at a reduced dose'. Smid also referred to EMA advice on 23 April 2010 that for patients on the reduced dose 'who demonstrated a deterioration of the disease physicians should consider restarting the original treatment with the full dose of Fabrazyme or switching to an alternative treatment, such as Replagal'.

With regard to the adverse events, Smid referred to an EMA assessment report (19 October 2010) on the shortage which noted an increase in reporting of adverse events since the start of the shortage, possibly due to the lowered dose. More specifically, it stated that: 'this pattern of adverse events resembles the natural, but accelerated, course of Fabry disease'. In addition, the post-marketing registry on outcomes of treatment with (the Fabrazyme Registry) showed that a higher percentage of reports was received of patients suffering from neuronopathic pains, diarrhoea and abdominal pain, compared to the period before the shortage.

Smid stated that the suggested increase in adverse events and complaints was difficult to interpret. It was possible that indeed a lower dose of agalsidase beta led to disease progression or to an accelerated disease course. However, it was also possible that the anxiety caused by the shortage and the recommendations by the EMA to treat patients at full dose of Fabrazyme in case of an adverse event, led to increased awareness and reporting of adverse events. Thus, there was a need for objective data to assess the impact of the shortage.

The Panel noted the EMA involvement regarding lowering the dose of Fabrazyme due to the supple shortage. It considered that this did not necessarily override the SPC. The Panel noted the promotional nature of the meeting. The reference to the unlicensed dose of Fabrazyme 0.5mg/kg monthly was

inconsistent with the SPC as alleged. A breach of Clause 3.2 was ruled. This ruling applied to Slide 12.

The Panel did not consider it was in itself misleading to show only the male patients. The patient population was 17 patients, 14 males and 3 females. There was no statistically significant difference in LysoGb3 increase after one year for females (p=0.3) whereas there was for males (p=0.001). This data was from a subset of patients. The Panel ruled no breach of Clause 7.2 on this narrow point.

With regard to the alleged failure to provide safety data the Panel noted Smid's comments about that data and the EMA Assessment Report 2010 set out above. Nevertheless, the Panel noted that the subject was not mentioned in the narrative, although according to Genzyme it was discussed at the meeting. The Panel noted that the slide had to be capable of standing alone. The Panel considered that as Slide 12 did not provide information on safety, Slide 12 was not balanced or based on an up-to-date evaluation of all the evidence. A breach of Clause 7.2 was ruled.

With regard to Slide 13 the Panel noted that there again was no safety data in relation to the consequences of switching. This study, Barranger *et al*, related to changing Replagal patients to Fabrazyme 1mg/kg. On balance, the Panel decided that Slide 13 was not similar to Slide 12 which referred to switching Fabrazyme 1mg/kg to Replagal 0.2mg/kg fortnightly or Fabrazyme 0.5mg/kg monthly. The Panel thus considered its comments above in relation to Slide 12 did not apply to Slide 13. The Panel noted that Barranger *et al* stated that 'its results do not support the safety of the switch and suggested that both products had common epitopes'. The Panel noted that Shire had not identified the safety consequences in relation to a switch to Fabrazyme 1mg/kg and further noted that it bore the burden of proof. The Panel therefore ruled no breach of Clause 7.2 in relation to Slide 13.

The Panel noted its rulings above in relation to Slide 12 and considered that consequently the graph failed to satisfy Clause 7.8. A breach of Clause 7.8 was ruled.

The Panel noted that Slide 13 was headed 'Switch study after recent FDA Replagal withdrawal'. The Panel noted that its comments above at Point A2 in relation to the statement 'US licence application unsuccessful again' were relevant. The Panel noted that the phrase presently at issue was different to that at Point A2. Nonetheless, the Panel considered that the phrase '… FDA Replagal withdrawal' was not sufficiently clear that Shire had withdrawn its application. It might be read that the FDA was the subject of the sentence. This was especially so given the message previously given by Slide 4. The statement 'Switch study after recent FDA Replagal withdrawal' was unclear and therefore misleading. A breach of Clause 7.2 was ruled. Given the audience and the purpose of the meeting of the Panel also considered the phrase disparaging to Replagal. A breach of Clause 8.1 was ruled.

APPEAL BY GENZYME

Genzyme repeated its view that Clauses 3.2, 7.2, 7.3, 7.4 and 7.8 did not apply to the information in Slides 12 and 13 since the information was not promotional. It, therefore, fell outside the scope of application of such requirements. As such, there were no grounds for a ruling by the Panel on the basis of Clauses 3.2, 7.2, 7.3, 7.4 and 7.8.

Concerning the ruling that the use of the term 'biosimilar' was misleading, Genzyme referred to its comments above about Slide 3.

Genzyme noted that the Panel ruled, on the allegation that it did not provide enough safety information, that Slide 12 was not up-to-date. Recalling the Panel's acknowledgement of the expertise of those present at the LSDEAG and the fact that the experts were already fully aware of the information presented, there could be no doubt that the experts knew about the potential risks of switching patients to a lower dose of Fabrazyme. In addition, the European Medicines Agency (EMA) assessment report discussed the consequences of the Fabrazyme shortage.

Genzyme submitted that the statement 'Switch study after recent FDA Replagal withdrawal' was used in good faith. It was intended to refer to the two applications that Shire withdrew from the FDA. Genzyme repeated that it did not intend to disparage Shire and its applications to the FDA. It was merely to provide historical context to the information presented in the slide. It was, therefore, incorrect to allege that the company disparaged Shire in this statement.

COMMENTS FROM SHIRE

Shire noted that Genzyme's presentation 1, Slides 12 and 13 included statements 'Consistent with biosimilarity and equivalent pharmacodynamics dose response' and 'An increased pharmacodynamic response with an increased dose of biosimilar ERT'. Shire alleged that this was misleading and could not substantiate biosimilarity and noted that the Panel had ruled a breach of Clauses 7.2, 7.3 and 7.4.

APPEAL BOARD RULING

The Appeal Board noted its previous comments and rulings about the use of the term 'biosimilar' (Point A1) and considered that they were relevant to Slides 12 and 13. Slide 12 featured the phrase 'Consistent with biosimilarity …' and Slide 13 referred to 'an increased dose of biosimilar ERT'. The Appeal Board considered that Slides 12 and 13 were misleading in this regard for the reasons set out at Point A1 and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3 and as the material did not substantiate the claim for biosimilarity the breach of Clause 7.4 was also upheld. The appeal was unsuccessful.

The reference to the unlicensed dose of Fabrazyme 0.5mg/kg monthly on Slide 12 was inconsistent with the SPC as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal was unsuccessful.

The Appeal Board noted that Slide 12 presented data following either changes in the dose of Fabrazyme or a switch from Fabrazyme to Replagal. These changes were a result of a supply shortage of Fabrazyme. The Appeal Board noted that the slide presented the effects on a surrogate marker for Fabry disease and yet unlike in the cited paper Smid *et al* there was no safety data presented in Slide 12. The Appeal Board considered that as Slide 12 did not provide information on safety, it was not balanced nor based on an up-to-date evaluation of all the evidence. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

The Appeal Board noted its rulings above in relation to Slide 12 and considered that consequently the graph failed to satisfy Clause 7.8. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8. The appeal was unsuccessful.

The Appeal Board noted that Slide 13 was headed 'Switch study after recent FDA Replagal withdrawal' and considered that its comments at Point A2 above in relation to the statement 'US licence application unsuccessful again' were relevant although the phrase now at issue was different. Nevertheless, the Appeal Board considered that the claim could be interpreted to mean that Replagal had been withdrawn by the FDA and not that Shire had withdrawn the application. Thus the Appeal Board considered that the statement 'Switch study after recent FDA Replagal withdrawal' was ambiguous and therefore misleading and given the audience and the purpose of the meeting, it disparaged Replagal. The Appeal Board upheld the Panel's rulings of a breach of Clause 7.2 and 8.1. The appeal was unsuccessful.

8 Slide 14 headed 'There are no published exceptions …'

COMPLAINT

Shire noted that Slide 14 stated 'Published data all show equivalent pharmacodynamic potency as expected from biosimilarity'.

The studies used in presentations 1 and 2 did not substantiate the claim of 'biosimilarity' as set out in the background information above. Shire alleged that the information presented was misleading and unbalanced in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Genzyme submitted that the comprehensive published data were presented in a balanced method without omission and all represented different components of experimental examination of 'biosimilarity'. The data were not capable of misleading this expert audience, but the presentation was designed to make an appropriate and valid point in the context of a scientific debate. The purpose of the headline was to make the statement that if there were any contradictory data which Genzyme had omitted they should be presented or indeed published. No other published or unpublished data were elicited. Contrary to Shire's assertions therefore the presentation was not unbalanced and misleading.

PANEL RULING

The Panel considered its ruling at Point A1 applied here. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

APPEAL BY GENZYME

Genzyme submitted that as established above when discussing Slide 3, 'biosimilar' had no very specific regulatory meaning. Its comments in relation to Slide 3 were of equal relevance to Slide 14.

COMMENTS FROM SHIRE

Shire had no specific comments in relation to Slide 14.

APPEAL BOARD RULING

The Appeal Board considered its ruling at Point A1 applied here. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2, 7.3 and 7.4. The appeal was unsuccessful.

9 Slide 15 headed 'Phase IV study of events ~50% risk reduction (conditional licence commitment)'

Slide 15 compared event rate in the intention to treat population against time for Fabrazyme vs placebo.

COMPLAINT

Shire stated that the graph detailed the number of 'events' (not labelled as adverse events) in patients receiving either placebo or Fabrazyme. The study and graph were not referenced, no dose was provided and no information regarding the actual adverse events to allow for an informed, clear and transparent risk assessment.

The supplementary information to Clause 7.2 stated:

> 'Referring only to relative risk, especially with regard to risk reduction, can make a medicine appear more effective than it actually is. In order to assess the clinical impact of an outcome, the reader also needs to know the absolute risk involved. In that regard, relative risk should never be referred to without also referring to the absolute risk. Absolute risk can be referred to in isolation.'

Shire alleged breaches of Clauses 7.2 and 7.6.

RESPONSE

Genzyme stated that the slide showed the primary efficacy data from Banikazemi *et al* (2007) which was the first reference in the narrative. The expert audience was fully familiar with this study. The point of calling it 'the Phase IV study of events' was for emphasis to achieve clarity of the regulatory situation in respect of 'unlicensed' or 'illegal' doses. The point being that for Fabrazyme, a Phase IV study of clinical outcome had been completed to fulfil obligations under the original European conditional

licence, whereas, in the case of Replagal, this obligation had not been fulfilled. Consequently, Fabrazyme had a full licence and Replagal still had a conditional licence with unfulfilled obligations as laid out in the narrative. The conditionally licensed situation of Replagal was therefore very similar to that of 0.3mg/kg of Fabrazyme for which 'the long term clinical relevance has not been established'.

Genzyme stated that it would have been scientifically incorrect to label the events as 'adverse events' as Shire seemed to assert should be the case. 'Events' were actually prospectively defined clinical events indicating deterioration of disease, as opposed to 'adverse events' in their totality. Genzyme rejected Shire's allegation that the presentation of event rates was potentially misleading; the actual event rate was shown on the Y-axis of the graph along with the estimated relative risk reduction (using proportional hazards). It was neither possible nor appropriate in the context of this 15 minute presentation to present all the details of all the studies.

In response to a request for further information from the Panel, Genzyme submitted that as defined in the study report (Banikazemi *et al*), 'The primary end point was the time to first clinical event (renal, cardiac, or cerebrovascular event or death) in the placebo and agalsidase-beta groups. We defined a renal event as a 33% increase in serum creatinine ... etc'.

The graph showed the absolute (clinical) event rate as percentage of the intention to treat population at risk for the placebo and treated groups and was clearly labelled as such on the Y-axis. The number of patients at risk at any time were shown below the X-axis. It could be seen that there were different numbers of patients in the two groups at risk, due to the 2:1 protocol defined randomisation. Because of this imbalance it was not only non-misleading but scientifically correct and appropriate to present the absolute event rates as a percentage of those at risk and show the actual numbers at risk below the X-axis.

The ~50% risk reduction referred to the estimated risk reduction between the groups (as calculated using a Cox proportional hazards analysis). It was simply incorrect to say that only the relative risk reduction was shown when the absolute risks were clearly shown on the graph which was fully and correctly labelled. There was nothing scientifically incorrect or misleading about this slide which was shown to an expert audience in the context of a 15 minute presentation. Genzyme denied the allegation of a breach of Clause 7.2.

PANEL RULING

The Panel queried whether the impression given by the slide which referred to 'risk reduction' and 'event rate' would be interpreted by the audience as defined clinical events indicating deterioration of disease as submitted by Genzyme in the absence of any such reference on the slide. It considered it would have been helpful to explain this on the slide. The Panel noted that contrary to Shire's assertion, the data presented in the graph was absolute event rates rather than relative rates, with the actual numbers at risk below the x axis. However, Genzyme's explanation on this point was absent from the slide.

The Panel noted that Banikazemi *et al* used the dose of 1mg/kg of Fabrazyme every two weeks for thirty-five months. It stated that the major limitation of the trial was the small sample size because of the rarity of the disease and the narrow window of disease severity necessary to quantify clinical benefit within a reasonable timeframe. Only one third experienced clinical events, six patients withdrew, eight patients had major protocol violations. The study concluded that Fabrazyme could slow the progression of serious life threatening complications of Fabry's disease even in patients who already had overt kidney dysfunction.

The Panel considered that the slide was misleading as insufficient information had been provided to give a clear summary of the data. The Panel ruled a breach of Clause 7.2. No reference had been provided to Banikazemi *et al* as required by Clause 7.6. The narrative included a reference to Banikazemi *et al* but this did not negate the need to include a reference on the slide. The Panel ruled a breach of Clause 7.6.

During its consideration of this allegation, the Panel was concerned about the reference to 'conditional licence commitment' and considered that this was a misleading way of differentiating between the products and the doses. There was no allegation in this regard. The Panel requested that Genzyme be advised of its views.

APPEAL BY GENZYME

Genzyme repeated its view that as the material provided to the SCT were not promotional, the requirements of Clauses 7.2 and 7.6 did not apply to Slide 15. As such, there were no grounds for a ruling by the Panel on the basis of Clauses 7.2 and 7.6.

Genzyme referred to the audience and that the experts were already fully familiar with Banikazemi *et al*, including the small sample size. The information on the slide could not be considered misleading.

COMMENTS FROM SHIRE

Shire had no specific comments in relation to Slide 15.

APPEAL BOARD RULING

The Appeal Board noted that Slide 15 was headed 'Phase IV study of events ~50% risk reduction (conditional licence commitment)' and included a graph of 'Event Rate in Intention-to-treat Population, %' against 'Time in study. *mo*'. The graph compared placebo and Fabrazyme and patient numbers were provided in a table below the graph. The Appeal Board considered that as there was no explanation of what the events were, the graph was not clear. The slide was misleading as insufficient information had been provided to give a clear summary of the safety data. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. No reference was provided

and the Appeal Board upheld the Panel's ruling of a breach of Clause 7.6. The appeal was unsuccessful.

10 Slide 16 headed 'Mehta A, Lancet (2009) depicts rates of decline of renal function for enzyme replacement therapies'

COMPLAINT

Shire stated that a graph from Mehta *et al* (2009) was presented with no clear contextual information. Shire alleged it was misleading not to state that the data was from a Fabry Outcome Survey (observational database) and this omission did not allow the audience to correctly interpret the data.

A separate Fabrazyme Phase III open label extension study was referenced in the graph using dashed lines. Replagal 0.2mg/kg was also used with a blue dashed line but with no reference. The graph presented did not have clear information as to the sources for each bar that were included as part of the original Mehta publication. Shire alleged that this data was therefore 'cherry-picked' to show misleading information.

Given the unbalanced nature of the information presented and the lack of clear context in the graph Shire alleged breaches of Clauses 7.2, 7.3, 7.6 and 7.8.

RESPONSE

Genzyme was surprised that Shire chose to criticise the appropriate reference to the figure from the Lancet publication which it sponsored and knew very well as did the clinical experts, one of whom corresponded with the Lancet about the publication. The narrative and discussion both set out to comprehensively show the available published evidence in respect of comparisons of the products. The authors decided to produce the comparative figure and the 'creation of the figures' in the Lancet article was attributed to a Shire employee.

Genzyme agreed that the figure was a complicated one and Genzyme had made 20 minute presentations about this figure alone, but this was a small part of a 15 minute presentation. Genzyme did not choose the comparison nor create the figure, but this comparison existed in the literature and to omit it would have been wrong. The method of presentation about which Shire complained simply highlighted that the rate of decline of renal function in male patients treated with 0.2mg/kg of enzyme replacement therapy (Replagal) was about the same rate as untreated male patients, whereas the rate of decline in patients treated with 1mg/kg enzyme replacement therapy (Fabrazyme) approached that of normal subjects. It would have been inappropriate to omit this comparison from the presentation and the method of presentation was not misleading to this expert audience which was familiar with the publication.

PANEL RULING

The Panel noted that no reference was included on the slide for the Replagal data and thus ruled a breach of Clauses 7.6 and 7.8.

Irrespective of the stated familiarity of some sectors of the audience with the publication the slide, nonetheless, had to comply with the Code. The Panel considered it would have been helpful to include details about the nature of the data and in this regard the slide was misleading. A breach of Clause 7.2 was ruled. The Panel noted Shire's allegation regarding 'cherry picking' the data but did not consider the company had provided sufficient detail in order to establish, on the balance of probabilities, that there had been a breach of the Code. The Panel ruled no breach of Clauses 7.2 and 7.3.

APPEAL BY GENZYME

Genzyme repeated its view that there were no grounds for a ruling by the Panel on the basis of Clauses 7.2, 7.6 and 7.8 in relation to the content of Slide 16. Genzyme noted the Panel's conclusion that the information presented would be interesting from a scientific view and it was likely that the audience would be aware of this data. In fact, the Panel relied on this consideration as a basis to conclude that the information in Slide 7 was not misleading. There was factually no difference between the Panel's reasoning for Slide 7 and Slide 16. The Panel, therefore, had an inconsistent approach in concluding that additional detail about the nature of the data was not relevant for Slide 7 although it was deemed necessary for Slide 16. Indeed, as previously submitted, not only were the experts fully aware of the Mehta *et al*, one of the experts even corresponded with the Lancet on the study. The presentation to the SCT was not misleading in any scientific sense.

COMMENTS FROM SHIRE

Shire had no specific comments in relation to Slide 16.

APPEAL BOARD RULING

The Appeal Board noted that no reference was included on the slide for the Replagal data and thus it upheld the Panel's rulings of a breach of Clauses 7.6 and 7.8. The appeal was unsuccessful.

The Appeal Board considered that details about the nature of the data should have been provided. The Appeal Board was concerned about the nature of the comparisons. The graph implied that there was a head-to-head study of Replagal and Fabrazyme and that was not so. The slide was misleading and the Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

11 Slides 17-20: 'Tondel *et al* (2013)'

Slide 17 set out the parameters for the study including dosage. There was a low dose group, Replagal 0.2mg/kg/every other week (eow) and Fabrazyme 0.2mg/kg eow. The high dose group was Fabrazyme 1mg/kg/eow, Replagal 0.4mg/kg/eow and Replagal 0.2mg/kg/week. Various results were given in Slides 18 and 19. Slide 18 plotted change in podocyte GL3-scores against cumulative agalsidase dose r=0.804, p=0.002. Slide 19 plotted the same variable against change in albumin-creatinine ratio.

Slide 20 was headed 'Tondel' and included two bullet points 'dose-response independent of ERT (alpha or beta)' and 'challenging the concept of similarity of the two licensed dose regimens', and the quotation '… similar milligram-to-milligram biochemical potency and clinical effect'.

COMPLAINT

Shire noted that Slide 17 referred to Fabrazyme 0.2mg/kg/every other week, Replagal 0.4/kg/ every other week and Replagal 0.2mg/kg/weekly. These doses were all inconsistent with the Fabrazyme and Replagal SPCs.

Slides 18 and 19 showed two different graphs which were unreferenced, unclear and did not provide clear context. The first showed a change in podocyte GL3-score vs cumulative agalsidase dose. The second graph showed the change in podocyte GL3-score vs the change in albumin-creatinine ratio. Shire alleged that the use of such graphs without context was misleading as the study was not powered to compare the efficacy and safety between Fabrazyme and Replagal.

Shire alleged that the information provided on Slides 17-19 did not substantiate the conclusions made on Slide 20. The study was not designed to provide the outcomes presented but were only observations made by the authors during the study thus rendering the Genzyme conclusions misleading.

Shire alleged breaches of Clauses 3.2, 7.2, 7.3, 7.4 and 7.8.

RESPONSE

Genzyme submitted that in the context of consideration of relative potency, the doses studied did not need to be those in the SPC. It would have been wrong to exclude these data from a clinical comparison using different methodology. The results which demonstrated milligram for milligram equipotency were a relevant component of the comprehensive data supporting the assertion that the two molecules were biologically highly similar. The clinical experts were all familiar with histological GL-3 scores and albumin-creatinine ratios, it was not possible to present all papers in detail in a 15 minute presentation.

PANEL RULING

The Panel noted its previous comments about the licensed doses of the two products in Point A2 above. Slide 17 was misleading and inconsistent with the SPC in this regard and a breach of Clauses 7.2, 7.3, 7.4 and 3.2 were ruled.

Slides 18 and 19 did not include any context. The Panel noted Genzyme's submission that the data was being used to demonstrate similar milligram to milligram potency. The Panel noted its comments regarding the licensed doses and considered that Slides 18 and 19 were contrary to the licensed doses. Slides 18 and 19 were misleading and each slide was ruled in breach of Clause 7.2. There was no reference on Slides 18 and 19. Each was ruled in breach of Clause 7.8.

The Panel noted its rulings above on Slides 18 and 19 and Shire's allegation that these slides did not substantiate the conclusions on Slide 20. Tondel *et al* stated that dose-response effect was seemingly independent of medicine type (alpha or beta). The authors referred to remarkable clearance of podocyte G3L-inclusions after 1 year of treatment with Replagal 0.4mg/kg every other week and only marginal effect in patients after treatment with the licensed dose of 0.2mg/kg every other week. Clinical progression of renal disease was not observed in either treatment group. The authors could not exclude that the lower Replagal dose had a beneficial effect on podocytes that could not be assessed by the scoring method used.

Tondel *et al* stated that the observations supported previous clinical studies that had shown dose-dependent effects on various surrogate endpoints indicating a higher efficiency of Fabrazyme 1mg/kg every other week than Replagal 0.2mg/kg every other week but further studies were needed to clarify the issue of equipotency of these medicines. The authors referred to a number of limitations including that treatments were not randomly assigned. The authors concluded that the findings were consistent with the hypothesis that Fabrazyme and Replagal had similar biologic activity per milligram and that studies in larger patient cohorts were necessary to confirm these observations. The Panel noted that Slide 20 did not reflect the relevant caveats within the study. The Panel considered that Slide 20 was misleading as alleged. A breach of Clause 7.2 was ruled.

APPEAL BY GENZYME

Genzyme repeated its view that there were no grounds for a ruling by the Panel concerning Slides 17-20 on the basis of Clauses 3.2, 7.2, 7.3, 7.4 and 7.8. Given the complexity of the facts leading to the initiation of this process, the Panel had not properly appreciated why Genzyme had originally engaged with the SCT. It was essential to understand that the debate concerning 0.3mg/kg of Fabrayzme had been going for some time. Genzyme provided an email from a senior Shire product specialist sent to a clinician in November 2012 when the rumours caused Genzyme most concern. It was then that Genzyme first approached the SCT about the issue. Genzyme stated that this email showed that while the origin of the rumours about its product during 2012 might not have emanated from Shire; the company certainly actively propagated them despite its statement that allegations were 'strongly refuted'.

Genzyme submitted that it had included evasive emails from Shire in its response, but the Panel had not properly interpreted their significance. The misleading rumours about the regulatory status arose after the national tender for Fabry enzyme replacement therapy commissioned by SCT (in its form as AGNSS at that time). An email demonstrated that Shire clearly called into question the status of 0.3mg/kg of Fabrazyme in comparison to 0.2mg/kg of Replagal including its regulatory status in the US.

With this background in mind, Genzyme had decided that it was necessary and critical to discuss the regulatory status during its presentation to the SCT.

Genzyme submitted that in addition, it rejected the ruling that because Slide 20 did not contain the caveats within the study cited, the information was misleading. The information presented was scientific and based upon a scientific journal that was substantiated and included the relevant caveats. To submit every caveat within the study for each statement or claim made, would be a futile exercise and would not further scientific exchange in the most meaningful manner within the fifteen minute time frame allocated. This conclusion was particularly relevant given the expertise of the audience. Moreover, nothing in Slide 20 was contrary to the caveats cited within the study itself. It was difficult to perceive that the information was misleading if there was no information in the first place that could be interpreted as being contrary to the caveats.

COMMENTS FROM SHIRE

Shire had no specific comments in relation to Slides 17-20.

APPEAL BOARD RULING

The Appeal Board noted its previous comments about the licensed doses of the two products in Point A2 above. Slide 17 was misleading and inconsistent with the SPC in this regard and the Appeal Board upheld the Panel's rulings of a breach of Clauses 7.2, 7.3 and 3.2. The appeal was unsuccessful.

With regard to Clause 7.4 the Appeal Board considered that as the data in Slide 17 was derived verbatim from its cited reference Tondel *et al*, and without any additional comment, the slide could be substantiated and thus on this very narrow ground it ruled no breach of Clause 7.4. The appeal on this point was successful.

The Appeal Board considered that as Slides 18 and 19 did not include any detail about the data presented therein they were very difficult to understand. Genzyme previously submitted that the data was used to demonstrate similar milligram to milligram potency. The slides were contrary to the licensed doses. The Appeal Board considered Slides 18 and 19 were misleading and upheld the Panel's ruling of a breach of Clause 7.2 in relation to each slide. Neither graph on Slides 18 or 19 was referenced and the Appeal Board upheld the Panel's ruling of a breach of Clause 7.8. The appeal was unsuccessful.

The Appeal Board agreed with the Panel ruling that Slide 20 did not reflect the relevant caveats within Tondel *et al*. Sufficient information needed to be provided to enable the reader to understand the data. It was not a question of simply not contradicting the caveats as submitted by Genzyme. The Appeal Board considered that Slide 20 was misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

12 Slide 21 headed 'My conclusions are:'

Slide 21 set out a number of conclusions including that the proteins were biosimilar on a mg for mg basis in all published data, that the clinical data and licensed situation was more robust for Fabrazyme 1mg/kg but difficult and incomplete for both. The slide also stated that there were no published data which 'gainsay biosimilarity' and that the 'cost savings of switching low dose patients are compelling'.

COMPLAINT

Shire alleged that the claim on Slide 21 that 'Fabrazyme (0.3mg/kg) provides 50% more protein' was misleading in implying that Fabrazyme was superior to Replagal. This claim was not clinically relevant, was a hanging comparison, misleading, unbalanced and was not referenced.

The slide also stated (in a larger font than that used in the rest of the presentation): 'Cost savings of switching low dose patients are compelling'.

Shire alleged that Genzyme's clearly intended to promote Fabrazyme by making unsubstantiated disguised promotional claims that Fabrazyme was more cost effective and to make misleading claims that the Fabrazyme data was more robust than for Replagal. In accordance with the supplementary information to Clause 7.2, for the economic evaluation of medicines to be acceptable as the basis of promotional claims, the assumptions made in an economic evaluation must be clinically appropriate. Shire alleged that the use of such claims in a non-promotional setting was in breach of Clause 12.

Shire submitted that Genzyme's assumptions were clinically incorrect and inconsistent with the Fabrazyme licence because the cost comparison was based upon the statement that all patients would be started and maintained on the 0.3mg/kg dose of Fabrazyme. This was not the case as no patients should be started on a 0.3mg/kg dose as per the Fabrazyme licence. Further, the maintenance dose was only acceptable for some patients and should not be generalised for all patients.

Given that the cost comparison was inappropriate and that the comparison between Replagal and the reduced Fabrazyme dose was not capable of substantiation, Shire alleged that the presentations 1 and 2 were misleading, disparaging, inconsistent with the SPC and in breach of Clauses 3.2, 7.2, 7.3 and 12.

RESPONSE

Genzyme noted that Shire had interpreted the statement 'Fabrazyme (0.3mg/kg) provides 50% more protein' as misleadingly implying that Fabrazyme was superior to Replagal, but it was clear that this was a simple statement of fact in comparison to 0.2mg/kg. There was no implication of superiority.

With regard to Shire's assertion that 'Genzyme's intention was to promote Fabrazyme by making unsubstantiated disguised promotional claims …' Genzyme stated that the objectives of the presentation were to:

1 Present all published comparisons of the two Fabry enzyme replacement therapies which formed a comprehensive body of data based on multiple experimental approaches which demonstrated milligram for milligram equivalence without exception.

2 Clarify misperceptions about the respective regulatory status of 0.2mg/kg, 0.3mg/kg and 1mg/kg of Fabry enzyme replacement therapy within the complex regulatory framework as it applied to ultra-rare diseases.

3 Present the relative costs per milligram of the different enzyme replacement therapies in the context of the tender to parties which were involved in the tender process.

4 Convert the four fold difference in price per milligram into cost per patient at the different licensed doses.

In achieving this objective it was necessary to give a factual, accurate and non-misleading account of the science concerning relative potency in accordance with Clause 1.2. These data necessarily concerned pharmacodynamic and clinical efficacy among other things. These statements of efficacy were made appropriately in a scientific context in a non-misleading and balanced way without omission. The statements were made to the SSCF and its LSDEAG in a properly convened meeting under Clause 1.2 in the context of commissioning considerations. Genzyme denied that this constituted promotion, disguised or otherwise or that any statement was unsubstantiated.

Genzyme agreed that a possible commissioning outcome based on this factual, accurate and non-misleading information would be to consider switching therapies and, in Genzyme's opinion, 'compelling' was a reasonable description of the potential cost savings in the context of NHS budgets. However, in this proper process based on the appropriate intention of the NHS Specialised Commissioning Function to have its expert advisory group interpret Genzyme's view of the science, it was not Genzyme's view that counted and the considerations were now going through the NHS processes for further assessment. Genzyme were not privy to these processes and would make no further input unless invited as was the case in this instance. This was all in the context of NHS England's need to make cost savings.

PANEL RULING

The Panel noted the comments previously made regarding the licensed dosage in Point A2 and in particular Point A3 wherein a ruling of a breach of Clauses 3.2 and 7.2 was made in relation to Slide 22.

The Panel was concerned that the conclusion 'Cost savings of switching low dose patients are compelling' on Slide 21 was misleading. This was compounded by Slide 22 headed 'ERT annual cost per 70kg patient at licensed dose'. The Panel noted that no account had been taken of the need to use 1mg/kg dose of Fabrazyme for six months before any consideration could be given to lowering the dose to 0.3mg/kg in certain patients and that the long-term clinical relevance of these findings had not been established. The Panel considered that Slide 21 was misleading in this regard and ruled breaches of Clauses 7.2 and 7.3.

It did not consider it was sufficiently clear whether the phrase 'clinical data and licensed situation are more robust for Fabrazyme 1.0mg/kg but difficult and incomplete for both' referred to Fabrazyme 0.3mg/kg or Replagal or both. It noted its comments above about the use of Fabrazyme 0.3mg/kg. A breach of Clauses 7.2 and 7.3 was ruled.

The claim that 'Fabrazyme 0.3mg/kg provides 50% more protein' was not clear as to what was being compared as alleged. The Panel ruled a breach of Clause 7.2 and 7.3.

The Panel noted the promotional nature of the activity and did not consider that Slide 21 was disguised promotion. No breach of Clause 12.1 was ruled.

APPEAL BY GENZYME

Genzyme repeated its view that as the material provided to the SCT was not promotional, the requirements of Clauses 7.2 and 7.3 did not apply to Slide 21. As such, there were no grounds for a ruling by the Panel on the basis of Clauses 7.2 and 7.3.

Genzyme submitted that the Panel's conclusion that the cost saving information provided in Slide 21 was misleading was incorrect. The purpose of the presentation was to provide information to the SCT to permit it to make an assessment of the cost saving for each product. As such, conclusions concerning potential cost savings arising from the use of Fabrazyme were not misleading but necessary and relevant given the context of the SCT meeting. Moreover, Genzyme's conclusions were provided in direct response to the SCT's request to provide such information. Genzyme understood, as was normal in the context of such meetings convened by the SCT, that its conclusions would be considered by the SCT for further assessment. The information was also provided within the context of the exemption in Clause 1.2. If the purpose of the exemptions in Clause 1.2 was to exclude such material from the definition of promotion, then it could be argued that the requirements in Clause 7.3 governing the format of comparisons in promotional material were not applicable. Genzyme asked the Appeal Board to clarify the scope of such exemptions.

Genzyme submitted that furthermore, the Panel's conclusion that Slide 21 was misleading due to the fact that there was a hanging comparison was incorrect. The statement 'Fabrazyme 0.3mg/kg provides 50% more protein' was a simple, direct comparison with Replagal 0.2mg/kg.

COMMENTS FROM SHIRE

Shire noted that it had raised concerns that the Genzyme presentation inappropriately promoted the switch of patients maintained upon Replagal to

low dose Fabrazyme using claims of biosimilarity when biosimilarity had not been demonstrated. Shire referred to the ABPI position paper on biosimilar medicines (issued May 2014); the second recommendation being:

> 'Automatic substitution is not appropriate for biological medicines including biosimilars. A biological medicine including a biosimilar, must only be substituted under the direct supervision and with the consent of the treating physician.
>
> Automatic substitution of one biological medicine for another can impact patient safety and makes post marketing surveillance more difficult as clear identification of the specific medicinal product is needed for appropriate PV monitoring.
>
> This is further supported by the British National Formulary (BNF) in their general guidance on prescribing, and also supported by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Biopharmaceutical Enterprises (EBE).
>
> The ABPI strongly recommends that automatic substitution should not apply to any biological medicine; this includes automatic substitution of a biosimilar for its reference biological medicine, or a biosimilar for another biosimilar where both have the same reference product. Substitution should only ever occur under direct supervision and consent of the treating physician and patients should be encouraged to speak to their doctor to address any questions about changes to their treatment.'

APPEAL BOARD RULING

The Appeal Board noted previous comments regarding the licensed doses, Point A2 (Slide 4) and Point A3 where Slide 22 was ruled in breach of Clauses 3.2 and 7.2.

The Appeal Board considered that the conclusion 'Cost savings of switching low dose patients are compelling' on Slide 21 was misleading. The Appeal Board noted that there were no low dose Replagal patients as its only licensed dose was 0.2mg/kg. The Appeal Board was extremely concerned about the use of 'compelling' given its comments on annual cost savings at Slides 6 and 22 (Point A3) above and the simplistic approach of this slide without any references to caution including patient safety issues related to switching. This was compounded by Slide 22 headed 'ERT annual cost per 70kg patient at licensed dose'. The Appeal Board noted that no account had been taken of the need to use 1mg/kg dose of Fabrazyme for six months before any consideration could be given to lowering the dose to 0.3mg/kg in certain patients and that the long-term clinical relevance of these findings had not been established. Slide 21 was misleading in this regard and the Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal was unsuccessful.

The Appeal Board did not consider it was sufficiently clear whether the phrase 'Clinical data and licensed situation are more robust for Fabrazyme 1.0mg/kg but difficult and incomplete for both' referred to Fabrazyme 0.3mg/kg or Replagal or both. It noted its comments above about the use of Fabrazyme 0.3mg/kg. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal was unsuccessful.

The claim that 'Fabrazyme 0.3mg/kg provides 50% more protein' was not clear as to what was being compared. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal was unsuccessful.

B The Genzyme narrative:

COMPLAINT

Shire noted the statement '… the pre-clinical and clinical data indicate that patients who are currently stable on low dose ERT (Replagal 0.2mg/kg) may be switched to Fabrazyme at a dose of 0.3mg/kg)'.

Shire stated that there were no published data showing the clinical benefits in switching stable patients from Replagal to 0.3mg/kg Fabrazyme. There was no correlation between the dose of different medicines and their clinical effect. Genzyme was not encouraging the rational use of a medicine in proposing that patients stable on Replagal were switched to 0.3mg/kg Fabrazyme. No balance was given by Genzyme to information concerning Fabrazyme's benefits and the risks associated with its use at this dose.

Shire alleged breaches of Clauses 7.2, 7.3, 7.4, 7.6, 7.10 and 8.

RESPONSE

Genzyme agreed with Shire that there were no published data showing the clinical benefits in switching stable patients from Replagal to 0.3mg/kg of Fabrazyme; the narrative and presentation showed that one would not expect a clinical improvement in undertaking such a switch, simply continued clinical stability in patients selected as suitable for low dose maintenance treatment. There would though be a significant impact on cost which might be relevant to commissioning considerations. Conversely in patients uncontrolled on low maintenance doses, there might be a clinical improvement in increasing the dose although to demonstrate this in a study would require large patient numbers and long observation periods, which were not feasible in the setting of an ultra-rare disease.

In conclusion, Genzyme stated that it had demonstrated that Clause 1.2 was in operation and that the narrative and presentation were factual, accurate and not misleading. The presentation was appropriate for this expert audience in the context of a meeting which was independently organised and chaired by officers of the Specialised Services Commissioning function at NHS England.

Genzyme stated that it rejected Shire's complaint in its entirety.

PANEL RULING

The Panel noted its comments about the nature of the meeting. It also considered its rulings above regarding the presentation were relevant to the narrative – particularly Point A2 above.

The Panel noted both companies agreed there was no published data on the clinical benefits of switching patients from Replagal to Fabrazyme 0.3mg/kg. The narrative did not include the qualifications given in the SPC. The Panel considered the narrative was misleading and a breach of Clauses 7.2 and 7.3 were ruled. The Panel also ruled a breach of Clause 7.4 due to the lack of clinical data to supporting a switch. A breach of Clause 7.10 was also ruled as the material did not encourage rational use.

With regard to the alleged breach of Clause 7.6 Shire had not identified what, in its view, needed to be referenced in the narrative. A list of references was given at the end of the document. Shire bore the burden of proof and it had not provided sufficient detail in this regard. The Panel ruled no breach of Clause 7.6. Similarly, Shire had not provided sufficient detail with regard to the alleged breach of Clause 8 and no breach of Clause 8.1 was ruled.

APPEAL BY GENZYME

Genzyme had no specific comments.

COMMENTS FROM SHIRE

Shire had no specific comments.

APPEAL BOARD RULING

The Appeal Board noted the Panel's comments about the nature of the meeting. The Appeal Board also considered its rulings at Point A above regarding the presentation were relevant to the narrative – particularly Point A2 above.

The Appeal Board noted that both companies agreed that there was no published data on the clinical benefits of switching patients from Replagal to Fabrazyme 0.3mg/kg. The narrative did not include the qualifications given in the Fabrazyme SPC. The Appeal Board considered the narrative was misleading and it upheld the Panel's rulings of a breach of Clauses 7.2 and 7.3. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.4 due to the lack of clinical data supporting a switch and consequently the Panel's ruling of a breach of 7.10 as the material did not encourage rational use. The appeal was unsuccessful.

C Summary

COMPLAINT

Shire stated that Genzyme had solicited a meeting with key stakeholders in sensitive commissioning roles within the NHS; the meeting was intended to be non-promotional. However, under the guise of providing a platform for a scientific debate, Genzyme, in fact, knowingly promoted Fabrazyme by providing cost information to the attendees. It also provided incorrect and misleading information during the meeting and prior to the meeting. The pre-circulated materials contained inaccurate and misleading content which it subsequently changed without making reference to these important areas before, during or after the meeting. These were uncertified materials.

Shire submitted that the delegates attended in the expectation of a scientific discussion but instead received promotional information about Fabrazyme and how much cheaper it would be compared with Replagal. The inclusion of direct cost comparisons and switch proposals based upon unfounded biosimilarity claims rendered Genzyme's actions misleading, inaccurate and disguised promotion.

Shire stated that Genzyme's narrative did not reflect the verbal information given or the detail contained within the slide deck used at the meeting. All documents must standalone and must meet Code standards. In Shire's view this was not the case as the narrative was received prior to the meeting and not referred to or linked to the presentation given.

In Shire's view, due to the significant breaches outlined above Genzyme had additionally breached Clauses 2 and 9.1 because it failed to maintain high standards and had discredited the industry.

Shire acknowledged a breach of Clause 2 was reserved for serious violations. Shire considered that Genzyme's actions constituted serious breaches of the Code. Shire noted that in particular the potential risks posed to patients by promoting the wholesale switch between the products on the basis of inconsistent claims which were not supported by robust clinical or supportive data. Shire considered that these actions brought discredit to, and reduced confidence in, the industry.

RESPONSE

In response to a request for further information regarding Clause 9.1 and 2, Genzyme submitted that the detailed account of the history and defence of the scientific allegations made by Shire showed that it had maintained very high standards throughout. Specifically it gave a detailed and clear account of:

1 Its interactions with the Specialised Services Commissioning Function at NHS England and its invitation to Genzyme to attend and make a presentation at the scheduled LSDEAG meeting.

2 Genzyme's willingness to share its materials in advance of the meeting which Shire did not.

3 Genzyme's willingness to engage in an open debate together with Shire and the LSDEAG in order to enable NHS England to clarify uncertainties and make sound commissioning decisions.

4 Genzyme's written and spoken communications of science, regulatory status of the products and their costs.

5 Genzyme's full, constructive and detailed engagement in inter-company dialogue including a comprehensive written response to all of Shire's concerns.

6 Genzyme's full and detailed response to Shire's complaint to the PMCPA which included many points which were not raised in intercompany dialogue.

Genzyme submitted that based on its previous response, it had clearly shown that it had maintained high standards at all times and therefore could not be considered to be in breach of Clause 9.1.

In response to an allegation of a breach of Clause 2, Genzyme submitted that it had not breached any clauses of the Code. Furthermore, it conducted the initial contact, the preliminaries and the preparation for both its meeting with representatives of NHS England and the subsequent meeting with the LSDEAG with integrity and in good faith.

Genzyme submitted that it approached the intercompany dialogue and Shire's multiple points of complaint with the same good faith, patience and integrity and therefore did not consider that there were any grounds for considering a breach of Clause 2. Genzyme submitted that it had clearly shown that it had done nothing to bring discredit upon or reduce confidence in the pharmaceutical industry and was confident that: it had not breached any clauses of the Code; it had acted in compliance with Clause 1.2 and all of its communications were factual, accurate and not misleading. In addition, it had maintained high standards at all times and acted in good faith and with integrity.

PANEL RULING

The Panel noted Shire alleged a breach of Clause 14.1 as the slides and narrative had not been certified. Genzyme submitted that the material was not written as promotional material but for the purpose of scientific debate. The material was not certified because of the operation of Clause 1.2. It was reviewed by Genzyme staff.

The Panel noted its comments above and that as the material was promotional it needed to be certified and this had not happened. The Panel ruled a breach of Clause 14.1.

The Panel noted its rulings above. It considered that Genzyme had not maintained a high standard and thus ruled a breach of Clause 9.1.

The Panel noted that Clause 2 was reserved for use as a sign of particular censure. The Panel noted the purpose of the meeting, including that it was to clarify information provided during a tender process and that the audience included experts in the field. The Panel was concerned that Genzyme had decided the material was non-promotional. The Panel also noted its rulings above that the material presented and pre-circulated was misleading, inconsistent with the Fabrazyme SPC and disparaging. On balance, the Panel considered that the circumstances brought discredit upon, and reduced confidence in, the pharmaceutical industry and thus ruled a breach of Clause 2.

APPEAL BY GENZYME

Genzyme submitted that it was a logical and justifiable conclusion that it was unnecessary for it to certify the material in accordance with Clause 14.1 because this requirement only applied to promotional materials. Genzyme stated that the submission of its narrative to the MHRA for review in advance of the meeting (upon which the MHRA made no comment) demonstrated its good faith and intention to uphold the highest standards throughout this procedure. The material was not written as promotional material, but for the purpose of the invited scientific debate with the expert advisory group to an NPO. For this reason the material was not reviewed and certified as promotional material after careful consideration of the operation of Clause 1.2 as explained in detail above. Moreover, as stated above it appeared that Shire did not certify its presentation as promotional either which confirmed Genzyme's view that Clause 1.2 applied to the meeting making it exempt from the requirement to certify. Further, Genzyme asked colleagues throughout the company to review the material to check the facts, NHS structures and referenced material.

Genzyme submitted that for these reasons and the fact that it had actively and diligently cooperated with all of the PMCPA's requests for further information, in addition to its willingness to communicate with Shire on all aspects of the alleged complaints, it submitted that it had maintained high standards at all times. Genzyme submitted that it had genuinely and honestly believed that the material provided to the SCT was not promotional as defined by the Code and did not contain inaccurate or misleading information. As such, Genzyme strongly rejected the Panel's ruling of breaches of Clauses 2 and 9.1.

Genzyme submitted that in considering possible breaches pertaining to 'high standards', 'discredit on the industry' or 'disparagement' (about regulatory status in the US) it was essential to understand the events and the background to Genzyme's concerns discussed above in relation to Slides 17-20. Whilst Shire 'strongly refuted this unfounded allegation' in its complaint, the rumours about the 'unlicensed status of doses' suited Shire's purposes. In addition to the email exchange with Shire, Genzyme also disclosed an internal Genzyme memorandum recording Shire's input to a meeting at the time these rumours were circulating. Genzyme now enclosed an email from Shire on the subject which demonstrated the company's active involvement in propagating the rumours. A member of the LSDEAG had supplied the email to Genzyme and the chairman of the LSDEAG could comment further.

Genzyme submitted that the discussions concerning Fabrazyme 0.3mg/kg vs Replagal 0.2mg/kg had been going on for about twelve months when its senior employee further sought the input of the SCT. This was vital from a commissioning point of view as

following the tender, Shire's 20% discount on its product was perceived as 'good value' when in fact Replagal, mg for mg, was four fold more expensive than Fabrazyme. Moreover, every published study failed to show any significant functional difference between the proteins, molecule for molecule. Genzyme's employee engaged properly with the responsible NPO; the SCT, resulting in the meeting with the LSDEAG.

Genzyme submitted that it had scrupulously followed the SCT's advice given by the chairman of the LSDEAG after consultation with fellow members of the SCT.

Genzyme emphasised this because the Panel had incorrectly concluded '…it appeared that the presentations and narrative might have gone beyond the original ambit of the meeting as evidenced by the email from LSDEAG' (sic; this was actually from the SCT) and went on to state 'In any event, the scope and content of the material and the emphasis on comparative costs was such that it appeared to be promotional'. In doing this it concluded that the exemption under Clause 1.2 was forfeited, whereas there was no such condition in the paragraph concerning NPOs upon which Genzyme relied in Clause 1.2. This was because the key matters in which the SCT was interested were cost and cost-effectiveness. Genzyme was specifically asked to address these issues along with the science and regulatory aspects which underlied the considerations of comparative cost-effectiveness. In doing this Genzyme also had to comply with the specific instruction of a '15 minute presentation as the basis for a scientific debate'. Genzyme's presentation precisely followed instructions from the chairman of the meeting convened by an NPO to properly inform commissioning decisions. Genzyme did nothing which could be construed as failing to maintain high standards and nothing which risked bringing discredit on the industry. The company had simply acted upon the request of the SCT and did not go beyond the scope of the meeting.

Genzyme submitted that it used the word 'biosimilar' so as not to repeat (continuously) the first sentence of the narrative 'Without exception, direct comparisons of the molecular properties of the two Fabry enzyme replacement therapies (ERT) demonstrate milligram for milligram equivalence (biosimilarity).' The word was clearly defined and then introduced for linguistic convenience and brevity in each slide of the presentation. This was appropriate for a scientific debate which was convened by an NPO.

Genzyme noted that the Panel had focused on the use of the word 'biosimilar' as misleading and therefore the presentation disqualified itself from Clause 1.2 which required content to be '…factual, accurate and not misleading'. Genzyme maintained that nobody was misled by the use of this word. This was supported in the letter from the member of the LSDEAG. Genzyme's presentation was properly constructed for the purpose of scientific debate by this expert audience. The chairman of the LSDEAG could comment further.

Genzyme submitted that the Panel incorrectly concluded that the exemption did not apply. Clause 1.2 was misinterpreted and two separate exemptions confused and therefore the findings of repeated breaches of Clauses 3.2, 7.2, 7.3, 7.4, 7.6, 7.8, 7.10 and 14.1 were incorrect and inappropriate. The presentation was made at a meeting of an NPO with its advisory group, therefore the only obligation under the Code was to be factual accurate and not mislead. The facts and the science were not presented in a misleading way and therefore there was no breach of the Code.

Genzyme submitted that even if the Panel disagreed with it on individual points about any alleged misleading statements, it was not justifiable to bring down the whole weight of the Code particularly Clauses 9 and 2. Genzyme had acted in good faith with an NPO, it had followed its instructions and it had not misled the audience. Genzyme's use of 'biosimilar' was not misleading and neither the presentation nor the narrative constituted promotional material as defined by the Code. Genzyme's scientific data in a difficult and specialised area was sound and its careful interpretation of the precise wording of Clause 1.2 was undertaken in complete good faith.

Genzyme submitted that further it engaged with Shire in inter-company dialogue in good faith in order to resolve this dispute to the satisfaction of both parties. Genzyme had met Shire for a whole morning and cancelled another engagement when it was clear that the inter-company meeting would over-run; it appeared that progress was being made towards a resolution. It transpired at this meeting that Shire had the previously circulated presentation which was missing a qualifying statement. Genzyme was not aware of this until then. Genzyme immediately explained what had happened therefore it was very surprised to see that Shire had made so much of something which had not misled those present at the time.

Genzyme submitted that at this meeting it stated that it would be prepared to give an undertaking that it would not describe the products as 'biosimilar' again. Genzyme offered this undertaking in good faith. Genzyme noted that Shire stated in its complaint that it did not subsequently provide the undertaking however this was very disingenuous because at the end of the meeting Shire did not accept the offer because it did not go far enough to resolve the issues. Genzyme asked Shire what would resolve the matter and it stated that it would write to Genzyme stating what it required. The written request, however, went much further than anything that had been discussed during the meeting or in inter-company dialogue and both parties quickly concluded that inter-company dialogue had not been successful.

Genzyme submitted that it was wrong to state that it had not maintained high standards or that it had brought discredit on the industry. Genzyme's account of events could be corroborated by the chairman of the LSDEAG in addition to the letter from the member of the LSDEAG.

COMMENTS FROM SHIRE

Despite Genzyme's appeal, Shire alleged that Genzyme had presented factually inaccurate, misleading and promotional material to the LSDEAG at a non-promotional meeting (instigated at Genzyme's request) held on 26 February 2014.

Furthermore, given the numerous failings to present data accurately in a balanced and non-promotional way, failing to recognize the context of the LSDEAG meeting and Genzyme's activities at the LSDEAG meeting, Shire agreed with the Panel ruling's of a breach of Clauses 9.1 and 2 on the basis that Genzyme failed to maintain high standards.

APPEAL BOARD RULING

The Appeal Board noted its decision above that the material at issue was promotional. It should have been certified. As neither the narrative nor the slides had been certified the Appeal Board upheld the Panel's ruling of a breach of Clause 14.1. The appeal was unsuccessful.

The Appeal Board noted its rulings at Points A and B above and considered that Genzyme had not maintained high standards. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal was unsuccessful.

The Appeal Board noted that Clause 2 was reserved for use as a sign of particular censure. The Appeal Board noted that the purpose of the meeting was, *inter alia*, to clarify information previously provided during an earlier tender process; the audience included experts in the field. The Appeal Board was astonished that Genzyme had considered that material provided subsequent to and directly related to a tender process was non-promotional. The Appeal Board was very concerned that regardless of whether Genzyme thought it could rely upon the exemption in Clause 1.2 for information submitted to national public organisations such as NICE, AWMSG and SMC, the quality standards in the Code relating to information claims and comparisons had not been applied to the material at issue. Much of Clause 7 applied broadly to all material, including that which was non-promotional rather than being limited to, promotional material as submitted by Genzyme. The Appeal Board noted its rulings above that the material presented and pre-circulated was misleading, inconsistent with the Fabrazyme SPC and disparaging. Genzyme had instigated the meeting. The Appeal Board was extremely concerned that Genzyme's material had focussed on the cost saving via a simple switch to a 0.3mg/kg dose of Fabrazyme without including the clear caveats in its SPC and no mention of important patient safety issues such as adverse events. It was also concerned about the conclusion that the cost savings of switching low dose patients were 'compelling'. The Appeal Board noted that the supplementary information to Clause 2 gave prejudicing patient safety as an example of an activity likely to lead to a breach of Clause 2. The Appeal Board considered that the circumstances brought discredit upon, and reduced confidence in, the pharmaceutical industry and it upheld the Panel's ruling of a breach of Clause 2. The appeal was unsuccessful.

The Appeal Board noted that the LSDEAG was the advisory group for the SCT which in effect could decide on commissioning at a national level. The potential gain to Genzyme in promoting a switch to 0.3mg/kg Fabrazyme was significant. The Appeal Board was so concerned about the content of the material at issue, its potential effects and impression given including the disregard for patient safety, that it decided, in accordance with Paragraph 10.6 of the Constitution and Procedure to require Genzyme to issue a corrective statement to all attendees at the LSDEAG meeting and all recipients of the pre-circulated material if they differed. The published case report should be provided. Details of the proposed content and mode and timing of dissemination of the corrective statement must be provided to the Appeal Board for approval prior to use. [The corrective statement appears at the end of the report]

The Appeal Board also decided that, given all of its concerns above, to require, in accordance with Paragraph 10.4 of the Constitution and Procedure, an audit of Genzyme's procedures in relation to the Code. The audit would take place as soon as possible. On receipt of the audit report and Genzyme's comments upon it, the Appeal Board would consider whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

Genzyme was audited in February 2015 and upon receipt of the audit report, the Appeal Board was extremely concerned that despite a very critical report which concluded with a number of specific recommendations, Genzyme's comments upon it were exceptionally brief. Indeed the Appeal Board considered that the brevity of the comments demonstrated a lack of engagement. With regard to the audit report, the Appeal Board was deeply concerned that the information which Genzyme had cascaded to its staff about the outcome of Case AUTH/2721/7/14 was not accurate or balanced; this was unacceptable. The Appeal Board considered that there was an apparent lack of insight and leadership with regard to compliance.

The Appeal Board requested, *inter alia*, a more detailed response to the audit report and additionally considered that Genzyme should be re-audited at the end of June 2015; on receipt of the report for that audit it would decide whether further sanctions were necessary.

On receipt of the more detailed response to the audit report from Genzyme, whilst the Appeal Board had some concerns, it would await the re-audit report before considering this matter further.

Upon receipt of that audit report, together with Genzyme's comments upon it the Appeal Board noted that although some progress had been made, further improvement was still required. The Appeal Board was concerned that some of Genzyme's anticipated

completion dates were long given the action required. Further, Genzyme had not given a completion date for implementation of some of the recommendations.

The Appeal Board was particularly concerned about some training material and considered that Genzyme needed to develop greater in-house expertise. The Appeal Board noted that Genzyme had plans in that regard and aimed to finalise updated materials by 31 August. It was hoped that updated standard operating procedures etc would be finalised by 30 November.

Notwithstanding the provision of certain materials in the meantime, the Appeal Board required that Genzyme be re-audited no later than early December 2015; on receipt of the report for that audit it would decide whether further sanctions were necessary.

Due to major organisational changes Genzyme requested that the re-audit be deferred until February 2016. The Appeal Board was reluctant to do so, given its concerns noted above, but it acknowledged the exceptional circumstances and on receipt of updated material from Genzyme, decided that the re-audit could be deferred until February 2016. Upon receipt of the report of the audit, together with Genzyme's (now Sanofi Genzyme) comments upon it, the Appeal Board noted that progress had been made since the audit in June 2015; the company had a new general manager and there had been a change in company structure. The audit report highlighted an improvement in company culture although concerns remained about Code training material that must be addressed. On the basis that this work was completed, the progress shown to date was continued and a company-wide commitment to compliance was maintained, the Appeal Board decided that, on balance, no further action was required.

Complaint received	**30 June 2014**
Undertaking received	**6 February 2015**
Appeal Board Consideration	**7 January 2015, 16 April, 14 May, 23 July, 9 September, 15 October, 17 March 2016**
Corrective statement issued	**18 March 2015**
Interim Case Report Published	**17 March 2015**
Case completed	**17 March 2016**

On 18 March 2015, Genzyme emailed the following corrective statement together with copies of the interim case report to those who had attended the advisory group meeting or who had received copies of Genzyme's materials prior to the meeting.

> 'On 26 February 2014, Genzyme Therapeutics Limited presented information about the use of Fabrazyme (agalsidase beta) in Fabry's Disease to a meeting of the Lysosomal Storage Disorders Expert Advisory Group (LSDEAG). I am writing to you because you were at that meeting and/or received papers provided by Genzyme for pre-circulation.
>
> Following a complaint by Shire Pharmaceuticals Limited under the ABPI Code of Practice for the Pharmaceutical Industry, the Code of Practice Appeal Board ruled that Genzyme's material was, *inter alia*, inaccurate, unbalanced and misleading. Particular concerns were raised about statements relating to the dose and cost of Fabrazyme vs Replagal (agalsidase alfa, marketed by Shire) and the description of the two as being 'biosimilar'. Some statements were inconsistent with the Fabrazyme summary of product characteristics (SPC). The materials thus fell short of the quality standards expected from a pharmaceutical company.
>
> As a result of the above, Genzyme has been required to circulate a copy of the published report for the case which contains full details and this is enclosed.
>
> Details of this case (Case AUTH/2721/7/14) are available on the PMCPA website (www.pmcpa.org.uk).'