

CODE OF PRACTICE REVIEW

The Prescription Medicines Code of Practice Authority (PMCPA) was established by The Association of the British Pharmaceutical Industry (ABPI) to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the ABPI. The PMCPA is a division of the ABPI which is a company limited by guarantee registered in England & Wales no 09826787, registered office 7th Floor, Southside, 105 Victoria Street, London SW1E 6QT.

COMPLAINTS AND NUMBER OF CASES CONSIDERED IN 2015

In 2015 the PMCPA received 54 complaints, compared with 51 in 2014. There were 80 in 2013, 78 complaints in 2012, 84 complaints in 2011, 86 complaints in 2010 and 92 complaints in 2009.

There were 66 cases to be considered in 2015, compared with 49 in 2014. The number of cases usually differs from the number of complaints because some complaints involve more than one company and others, for a variety of reasons, do not become cases at all.

The number of complaints from health professionals in 2015 (10) was less than the number from pharmaceutical companies (both members and non members of the ABPI) (12). In addition there were six complaints from anonymous health professionals. The more complex cases considered by the Authority are generally inter-company complaints which often raise a number of issues.

There were two complaints made by employees/ex-employees.

Eight complaints were nominally made by the Director and four arose from voluntary admissions by companies. There were two cases arising from alleged breaches of undertakings. One case arose from criticism in the media and another from publication of a study looking at disclosure of clinical trial details.

There were 16 anonymous complaints in addition to the six from anonymous health professionals. Two were from anonymous employees.

The details will be included in the PMCPA 2015 Annual Report which will be published shortly.

NEW INDEPENDENT APPEAL BOARD MEMBER

The ABPI Board has appointed Mr Andrew White as a member of the PMCPA Appeal Board from an independent body involved in providing information on medicines. Mr White is Head of Medicines Optimisation at NHS Greater Manchester Shared Service.

PUBLIC REPRIMAND FOR ASTRAZENECA

AstraZeneca UK Limited has been publicly reprimanded by the Code of Practice Appeal Board for providing inaccurate information to the Code of Practice Panel (Case AUTH/2793/9/15).

In Case AUTH/2793/9/15, the Panel ruled breaches of the Code with regard to a leavepiece which provided misleading instructions on how to use the EMIS Web clinical system such that controlled (based on HbA1c levels) type 2 diabetic patients might be inappropriately treated with Forxiga (dapagliflozin). AstraZeneca accepted the Panel's rulings and provided the requisite undertaking. When informed of the outcome of the case, the complainant noted that AstraZeneca's response to the Panel was inaccurate with regard to how EMIS could be searched. AstraZeneca initially stood by the information it had submitted but on the provision of further and better particulars from the complainant, it subsequently accepted that the information it had provided was incorrect.

The Panel reported AstraZeneca to the Appeal Board. On consideration of that report the Appeal Board noted that AstraZeneca had relied wholly on the expertise of an agency when drawing up the leavepiece and had demonstrated extremely poor governance in the matter. This was not acceptable. The Appeal Board noted that AstraZeneca had taken full responsibilities for its failings but, nonetheless, considered that it was fundamental for effective self-regulation that companies provide accurate information to the Panel.

Full details of Case AUTH/2793/9/15, including a corrective statement, can be found on page 56 of this issue of the Review.

DISCLOSURE DEADLINE – 30 JUNE 2016

The ABPI central platform disclosing details of certain transfers of value will go live by 30 June 2016. Details can be found in the Code (Clause 24 and others) and on the ABPI website. Other countries in Europe will also disclose by 30 June 2016.

The 2016 updated 'e-learning for health professionals' available on our website includes more information about the ABPI central platform for disclosure so that health professionals can understand the relevant requirements in the Code.

CODE OF PRACTICE TRAINING

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

These full day seminars offer lectures on the Code and the procedures under which complaints are considered, discussion of case studies in syndicate groups and the opportunity to put questions to the Code of Practice Authority.

The next Code of Practice seminar dates on which places remain available are:

Thursday 6 October 2016
Monday 5 December 2016

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

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

HOW TO CONTACT THE AUTHORITY

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

Telephone: 020 7747 8880
Facsimile: 020 7747 8881

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

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

Heather Simmonds: 020 7747 1438
Etta Logan: 020 7747 1405
Jane Landles: 020 7747 1415
Tannyth Cox: 020 7747 8883

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

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

UPDATED ADVICE AND GUIDANCE: ADVISORY BOARDS AND DIGITAL COMMUNICATIONS

In April the PMCPA published updated advice and guidance including on advisory boards.

The arrangements for advisory board meetings are often the subject of requests to the PMCPA for informal advice, and are also discussed with companies when audits are carried out by the Authority. The updated advice includes points to consider to ensure that advisory boards meet the requirements of the Code and that the relevant information is available when assessing proposals. The points to consider reflect what information might be required in the event that a company has to respond to a complaint under the Code.

The guidance stresses that it is acceptable for companies to arrange advisory board meetings and the like, and to pay health professionals and others for advice on subjects relevant to their products. Advisory boards should only be held to enable companies to answer legitimate business questions to which they do not already know the answer. Companies are asked to cascade the guidance to regional and global colleagues to increase understanding and to emphasise the importance of ensuring that arrangements for advisory boards are appropriate.

The PMCPA Digital Guidance highlights relevant 2016 Code requirements and includes a series of frequently asked questions and answers.

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 unsubstantiated 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 uptake. Slide 9 headed 'Sakuraba [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 (EMA/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 Genzyme'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 unsubstantiated 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 biosimilars 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 Fabrazyme 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 Fabrazyme 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 licence 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 'Sakuraba [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 *et 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 'Sakuraba [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 (EMA/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 neuropathic 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 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 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 Fabrazyme 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 stand alone 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 the 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).

ANONYMOUS, NON-CONTACTABLE EX-EMPLOYEE v CHUGAI

Consultancy arrangements

An anonymous, non-contactable complainant who described themselves as an ex-employee and as the complainant in Case AUTH/2749/2/15, contacted the Authority stating that he/she was disappointed in the outcome of that case. The complainant noted the Panel's reference to the previous complaint not being backed with any evidence. In light of this, the complainant submitted a complaint that was closely similar to that in Case AUTH/2749/2/15 and referred to specific pieces of new evidence that were available to support this complaint but did not provide any of them. The complainant hoped Chugai would conduct a more rigorous investigation this time.

A summary of the detailed response from Chugai is given below.

The Panel noted that anonymous and non-contactable complaints were accepted and like all complaints, judged on the evidence provided by the parties. Complainants had the burden of proving their complaint on the balance of probabilities.

The Panel noted that Case AUTH/2749/2/15 included *inter alia*, allegations about consultancy arrangements with a named individual. In that case, the Panel had ruled a breach of the Code on one matter but no breach of the Code on other matters raised. The Panel had made it clear that the complainant had not provided any evidence to support his/her allegations.

The Panel noted Chugai's comments about the decision under Paragraph 5.2 of the Constitution and Procedure to allow the present complaint to proceed. Paragraph 5.2 detailed the situations where a matter closely similar to one which had been the subject of a previous adjudication could be allowed to proceed: these were, at the discretion of the Director, where new evidence was adduced or if the passage of time or change in circumstances raised doubts as to whether the same decision would be made about the current complaint. The Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Panel where no breach of the Code was ruled and which was not the subject of appeal. The case preparation manager had noted that the no breach rulings in the previous case were not the subject of an appeal and thus referred the entire case to the Panel for consideration.

The Panel noted that it was not possible to contact the complainant for more information. The complaint appeared to consist largely of references to evidence which the complainant had not provided. Given the Constitution and Procedure and that the previous case had made both the burden of proof, and the

need for the complainant to provide evidence clear, the Panel queried why no evidence had been provided in the present case. The burden was firmly on the complainant in that regard.

Noting its comments above and the complete absence of evidence the Panel considered that as in the previous case the complainant had failed to demonstrate a breach of the Code on several matters. No breach of the Code was ruled.

The Panel noted, however, that the previous case included a ruling of a breach of the Code in relation to one matter regarding the arrangements with the consultant and considered that the rulings in the previous case about the consultancy applied here including the breach of the Code. This ruling was appealed by Chugai.

The Panel noted that in the previous case, although it had some concerns about the consultancy arrangements it considered that Chugai had not brought discredit upon, or reduced confidence in the pharmaceutical industry. The Panel noted its rulings above in the present case and again ruled no breach of Clause 2.

The Panel did not consider that the complainant had shown that Chugai's response to Case AUTH/2749/2/15 was inadequate; no breach of the Code was ruled. In the Panel's view the manner in which Chugai had responded to Case AUTH/2749/2/15 was not such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

With regard to Chugai's appeal, the Appeal Board noted Paragraph 5.2 of the Constitution and Procedure included:

'If a complaint concerns a matter closely similar to one which has been the subject of a previous adjudication, it may be allowed to proceed at the discretion of the Director if new evidence is adduced by the complainant or if the passage of time or a change in circumstances raises doubts as to whether the same decision would be made in respect of the current complaint. The Director should normally allow a complaint to proceed if it covers matters similar to those in a decision of the Panel where no breach of the Code was ruled and which was not the subject of appeal to the Appeal Board.'

The Appeal Board noted that the case preparation manager appeared to have relied only on the second sentence so that as no breach of the Code

had been ruled in Case AUTH/2749/2/15, the matters now at issue in Case AUTH/2790/8/15 were referred to the Panel.

In the Appeal Board's view the first sentence of the relevant section of Paragraph 5.2 above was a condition precedent. The Director had to decide that the conditions set out in that sentence had been met before exercising any discretion as to whether a complaint about a matter closely similar to one which had been the subject of a previous adjudication should be allowed to proceed.

The Appeal Board noted that the matters now at issue were closely similar to those raised in Case AUTH/2749/2/15. The questions to be considered were 'Had new evidence been adduced?' or 'Had the passage of time or a change in circumstances raised doubts as to whether the same decision would be made?'. The Appeal Board considered that no new evidence had been provided by the anonymous complainant who, as previously, had chosen to be non-contactable. The Appeal Board considered that this was extremely regrettable given that in Case AUTH/2749/2/15 the Panel had criticised the lack of evidence provided by the complainant and had noted that he/she had the burden of proving his/her complaint on the balance of probabilities. The Appeal Board also noted that the complainant referred to providing evidence upon publication of the Panel's ruling. The complainant should have provided any such evidence with the complaint. The Appeal Board noted that Chugai had not identified any new material in its response to Case AUTH/2790/8/15. The Appeal Board noted that the current complaint was received only three months after the completion of the previous case and there was apparently no change in circumstances. In the Appeal Board's view, therefore in relation to the first part of the sentence in Paragraph 5.2, the case preparation manager should have decided that neither condition precedent had been met and so the exercise of the Director's discretion in relation to the second sentence did not arise. The complaint should not have proceeded. Consequently, there could be no breach of the Code.

An anonymous, non-contactable complainant who described themselves as an ex-employee and as the complainant in Case AUTH/2749/2/15, contacted the Authority stating that he/she was disappointed in the outcome of that case. Case AUTH/2749/2/15 concerned, *inter alia*, the use of a consultant. The complainant in that case had not been able to appeal the Panel's rulings of no breach of the Code as he/she was non-contactable.

COMPLAINT

In summary, the complainant referred to Case AUTH/2749/2/15 and noted the Panel's reference to his/her previous complaint not being backed with any evidence. In light of this the complainant alleged that new evidence was available to support this fresh set of allegations about the use of a consultant and listed some of the evidence available but provided none. The complainant referred to legal advice received which directed him/her to make this fresh set of allegations

and to provide all evidence upon publication of the Panel's ruling in the hope that Chugai would conduct a more rigorous investigation.

When writing to Chugai the Authority asked it to respond to the requirements of Clauses 2, 9.1, 18.1, 21, 22 and 23.1 in relation to the consultancy arrangements and Clauses 2 and 9.1 in relation to the implied allegation that Chugai's investigation into the previous complaint was not sufficiently rigorous.

RESPONSE

In summary, Chugai submitted that this complaint raised no new issues to those raised in Case AUTH/2749/2/15, but simply disputed the Panel's findings in that case and referred to additional evidence (which had not been disclosed) in relation to the same matters. While Chugai accepted that the Director had a discretion (under Paragraph 5.2 of the Constitution and Procedure), to allow a complaint to proceed, even where it concerned a matter closely similar to one that had been the subject of a previous adjudication if (i) new evidence had been adduced or (ii) the passage of time or a change in circumstances raised doubts as to whether the same decision would be made in respect of the current complaint, this case was the same, rather than 'closely similar' to Case AUTH/2749/2/15, no new evidence had in fact been adduced beyond the references to the existence of evidence set out in the second complaint and there was no passage of time or change in circumstances to cast doubt on the original decision. Paragraph 5.2 further stated that the Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Panel where no breach of the Code was ruled and which was not the subject of an appeal. In this instance however, a breach of the Code was ruled in Case AUTH/2749/2/15.

Chugai therefore submitted that the current complaint was an abuse of process as it sought to reopen matters previously ruled upon by the Panel in Case AUTH/2749/2/15, which had already been investigated and decided. Chugai thus requested the Director to reconsider the decision to proceed with the current complaint.

Chugai stated that all of the matters raised in this complaint were previously ruled upon by the Panel in Case AUTH/2749/2/15, were *res judicata* and should not be the subject of further proceedings.

However, and despite this view, Chugai had nevertheless conducted a focused and rigorous re-investigation regarding arrangements with the consultant. Details were provided to show that no evidence was found to suggest the previous response to refute the claim was incorrect or to alter the response to Case AUTH/2749/2/15.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints, judged on the evidence provided by the parties. Complainants had

the burden of proving their complaint on the balance of probabilities.

In summary, the Panel noted that the previous case, Case AUTH/2749/2/15, concerned allegations, *inter alia*, about consultancy arrangements with a named individual. In that case, the Panel had ruled a breach of Clause 9.1 in relation to one matter but no breach of the Code in relation to the remaining allegations. The Panel had made it clear that the complainant had not provided any evidence to support his/her claim. As the complainant in that case was non-contactable he/she was not able to appeal the rulings of no breach of the Code. The Panel noted that the previous case, Case AUTH/2749/2/15, had now been published. The complainant in the present case, Case AUTH/2790/8/15, had stated that he/she was also the complainant in the previous case but the Panel noted that there was no way of verifying whether that was so.

The Panel noted Chugai's comments about the decision under Paragraph 5.2 of the Constitution and Procedure to allow the present complaint to proceed. The Panel noted Paragraph 5.2 detailed the situations where a matter closely similar to one which had been the subject of a previous adjudication could be allowed to proceed: these were, at the discretion of the Director, where new evidence was adduced or if the passage of time or change in circumstances raised doubts as to whether the same decision would be made about the current complaint. The Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Panel where no breach of the Code was ruled and which was not the subject of appeal. The case preparation manager had noted that the no breach rulings in the previous case were not the subject of an appeal and thus referred the entire case to the Panel for consideration.

The Panel noted that it was not possible to contact the complainant for more information. The complaint appeared to consist largely of references to evidence which the complainant had not provided. Given the Constitution and Procedure and that the previous case had made both the burden of proof and the need for the complainant to provide evidence clear, the Panel queried why no evidence had been provided in the present case. It was not, as implied by the complainant, for Chugai to provide the requisite evidence although it should submit a complete response. The burden was firmly on the complainant in that regard. The failure to adduce evidence was, in the Panel's view, odd given the complainant's reference to legal advice.

Noting its comments above and the complete absence of evidence the Panel considered that as in the previous case the complainant had failed to show that there had a breach of the Code in most of the matters he/she raised with regard to the engagement of a consultant. No breaches of the Code were ruled as in Case AUTH/2749/2/15.

The Panel noted, however, that the previous case included a ruling of a breach of Clause 9.1 in relation to one matter. The Panel noted that the rulings in the previous case about the consultancy applied here

including the breach of Clause 9.1. This ruling was appealed by Chugai.

The Panel noted that in the previous case, Case AUTH/2749/2/15, although it had some concerns about the consultancy arrangements it considered that Chugai had not brought discredit upon, or reduced confidence in the pharmaceutical industry. The Panel noted its rulings above in the present case and again ruled no breach of Clause 2.

In relation to the implied allegation that Chugai's investigation into the previous complaint was not sufficiently rigorous, the Panel noted that the company's response had been wide ranging and detailed. The Panel did not consider that the complainant had shown that the company's response to Case AUTH/2749/2/15 was inadequate. In that regard the Panel ruled no breach of Clause 9.1. In the Panel's view the manner in which Chugai had responded to Case AUTH/2749/2/15 was not such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

APPEAL BY CHUGAI

Whilst Chugai did not appeal the Panel's rulings in Case AUTH/2749/2/15 and did not challenge the findings of the Panel that no new breaches of the Code were established as a result of the second complaint in the current case, Chugai submitted that the procedure followed by the PMCPA in relation to these two complaints was unfair and did not reflect the Constitution and Procedure. In particular, Chugai was concerned that the Panel's approach in Case AUTH/2790/8/15 could result in unlimited further complaints by the same complainant raising the same allegations, unsupported by evidence, each admitted by the PMCPA for consideration by the Panel and each resulting in a repeat of the ruling of a breach of Clause 9.1, found in Case AUTH/2749/2/15.

This appeal therefore related to the PMCPA's decision to refer the second complaint to the Panel and the fact that the breach of the Code in Case AUTH/2749/2/15 was repeated in Case AUTH/2790/8/15 with the requirement of a further undertaking and that the published decision of the Panel would, seemingly, suggest a second finding of breach of Clause 9.1 even though, no new breach of the Code arising from the second complaint, had been ruled.

Chugai submitted detailed reasons as to why it considered that this case should not have proceeded.

In summary, Chugai alleged that the second complaint, submitted with no new evidence adduced, a mere three months after the conclusions of the Panel following the first complaint, was an abuse of process and that the issues considered by the Panel in Case AUTH/2749/2/15 were *res judicata* and might not be reopened.

Chugai therefore asked the Appeal Board to conclude:

- that the second complaint should not have been admitted by the Director for consideration by the Panel;

- that, in the absence of any new evidence, any finding of a breach of Clause 9.1 in the context of Case AUTH/2790/8/15 should be quashed;
- that the Panel's request for a second undertaking and assurance by Chugai arising from the finding of the Panel in Case AUTH/2749/2/15 was inappropriate and unnecessary and there should be no further administrative charge;
- if the Appeal Board concluded in favour of the proposal that Case AUTH/2790/8/15 should not have been referred to the Panel then no summary would be published;
- if the Appeal Board did not find in favour of the above proposal then the summary of Case AUTH/2749/2/15 published by the PMCPA should make clear that no new breach of Clause 9.1 was ruled and that the finding in Case AUTH/2749/2/15 might be referenced, the finding had not been repeated.

APPEAL BOARD RULING

The Appeal Board noted Paragraph 5.2 of the Constitution and Procedure included:

'If a complaint concerns a matter closely similar to one which has been the subject of a previous adjudication, it may be allowed to proceed at the discretion of the Director if new evidence is adduced by the complainant or if the passage of time or a change in circumstances raises doubts as to whether the same decision would be made in respect of the current complaint. The Director should normally allow a complaint to proceed if it covers matters similar to those in a decision of the Panel where no breach of the Code was ruled and which was not the subject of appeal to the Appeal Board.'

The Appeal Board noted that the case preparation manager appeared to have relied only on the second sentence in relation to whether the complaint should proceed. The case preparation manager's response to Chugai's submission that the complaint should not proceed to the Panel stated that as no breach of the Code had been ruled in Case AUTH/2749/2/15, the matters now at issue in Case AUTH/2790/8/15 had been referred to the Panel.

In the Appeal Board's view the first sentence of the relevant section of Paragraph 5.2 above was a condition precedent. The Director had to decide that the conditions set out in that sentence had been met before exercising any discretion as to whether a complaint about a matter closely similar to one which had been the subject of a previous adjudication should be allowed to proceed.

The Appeal Board noted that the matters now at issue were closely similar to those raised by someone who appeared to be the same complainant as in Case AUTH/2749/2/15. The questions to be considered were 'Had new evidence been adduced?' or 'Had the passage of time or a change in circumstances raised doubts as to whether the same decision would be made?'. The Appeal Board considered that no new evidence had been provided by the anonymous complainant who, as previously, had chosen to be non-contactable. The Appeal Board considered that this was extremely regrettable given that in Case AUTH/2749/2/15 the Panel had been critical of the lack of evidence provided by the complainant and had noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. The Appeal Board also noted that the complainant referred to legal advice which included providing evidence upon publication of the Panel's ruling. The complainant should have provided any such evidence with the complaint. The Appeal Board noted that Chugai had not identified any new material in its response to Case AUTH/2790/8/15. The Appeal Board noted that the current complaint was received only three months after the completion of the previous case and there was apparently no change in circumstances. In the Appeal Board's view, therefore in relation to the first part of the sentence in Paragraph 5.2, the case preparation manager should have decided that neither condition precedent had been met and so the exercise of the Director's discretion in relation to the second sentence did not arise. The complaint should not have proceeded. Consequently, there could be no breach of Clause 9.1.

Complaint received	14 August 2015
Case completed	21 January 2016

CLINICAL PHARMACIST v ASTRAZENECA

Identifying patients suitable for Forxiga treatment and failing to provide an accurate response to the Panel

A clinical pharmacist complained about an AstraZeneca leavepiece about how to create a clinical system search to identify patients suitable for treatment with Forxiga (dapagliflozin).

Forxiga was indicated in adults with type 2 diabetes to improve glycaemic control as monotherapy when diet and exercise alone did not provide adequate glycaemic control in patients for whom use of metformin was considered inappropriate due to intolerance. It was also indicated in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, did not provide adequate glycaemic control.

The leavepiece was entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. The front page included 'FORXIGA is not indicated for weight loss and is not recommended for use in patients with an [eGFR] < 60 mL/min/1.73m². FORXIGA is not licensed for use with thiazolidinedione or GLP-1 agonists'.

The complainant alleged that the search instructions were potentially misleading and could easily identify patients who would not be suitable for treatment. The instructions showed how to add criteria for body mass index (BMI), glomerular filtration rate (GFR) and glycosylated haemoglobin (HbA1c). In all cases a clinical code was added with a qualifying value. However, no time restriction was added to qualify these values. The complainant explained the flaw. Patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. However, the value should also be the most recently recorded. A patient with an HbA1c of 48 now who had previously had an HbA1c of 63 should not be included in the final search. However, by applying the instruction as specified they would be included for consideration.

The complainant alleged that whilst he/she hoped that a clinical review would subsequently deem the patient as inappropriate for treatment, the search instructions could be construed as misleading by including such patients. By creating a sub-optimal search the usual high standards demonstrated by the pharmaceutical industry had not been maintained.

The detailed response from AstraZeneca is given below.

The Panel noted that the search was described in 9 steps: Setup initial search; Add Age Range to Search; Add Read Code to Search; Add Medication to Search; Add BMI to Search; Add HbA1c to search; Add GFR to search; Save and Run Report; and Build Report Output.

Each step included detailed instructions and some included screenshot examples.

The Panel noted the order of the search criteria, age, read code, and medication were followed by BMI before selecting HbA1c and GFR. The report was then run (Step 8). Step 9, Build Report Output, instructed users to add BMI (22K) and value ≥ 25 before adding columns for HbA1c and GFR but unlike BMI no values were listed for these two criteria at this step in the description in the leavepiece. In the example screenshot of the completed report which appeared below step 9, the column of BMI values was fully populated for each identified patient and appeared before the HbA1c column. Neither the HbA1c nor GFR columns were fully populated. The Panel noted AstraZeneca's submission that the example report was generated using dummy patients in a test system and a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated. The Panel considered that this was not clear from the leavepiece and was compounded by the screenshot heading 'The completed report should resemble this screenshot'. The Panel accepted AstraZeneca's submission regarding the responsibility of prescribers to make clinically reasoned prescribing decisions but considered that it was important that both the instructions and information on the nature and interpretation of the data retrieved was abundantly clear and otherwise complied with the Code. In this regard the Panel was concerned that nowhere in the leavepiece was there any mention of carrying out a clinical review nor was it referred to in the verbal briefing to the diabetes sales leadership team. In the Panel's view, the leavepiece implied that following the 9 step guide would generate a list of uncontrolled patients with a BMI ≥ 25 who were suitable for Forxiga. This would include patients who currently had an HbA1c value of less than 58 but who previously had a value of more than 58 being identified as 'uncontrolled'. This impression was compounded by the title '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. In the Panel's view it might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. The Panel considered that the leavepiece was misleading and a breach was ruled.

Whilst the Panel noted that BMI was relevant to this therapeutic area, the emphasis on BMI in the title, search criteria and the example completed report screenshot which omitted HbA1c values and the failure to refer to the need to carry out a clinical review meant that Forxiga had been promoted for some patients based solely on their weight.

Forxiga was not indicated for weight loss. A breach was ruled.

The Panel however did not consider that the instructions were misleading on the narrow point that no time restrictions were included in the search criteria for BMI, GFR and HbA1c as alleged. No breach was ruled.

The Panel considered that high standards had not been maintained and a breach was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure.

Following notification of the outcome of the case, the complainant noted that, in its response, AstraZeneca had provided inaccurate information about how EMIS could be searched. AstraZeneca initially responded that the information, which it could not validate, was provided by an agency; the agency had confirmed its understanding of the search capabilities of the EMIS system. The complainant was informed and subsequently provided further and better particulars which were provided to AstraZeneca. The company subsequently accepted that the information it had provided was incorrect.

Detailed comments from the complainant and AstraZeneca are given below.

Following receipt of the additional information from both parties the Authority asked AstraZeneca to respond including in relation to a possible report under Paragraph 8.2 of the Constitution and Procedure.

The original Panel reconvened and considered the matter in relation to Paragraph 8.2 of the Constitution and Procedure. The Panel noted that AstraZeneca had provided the requisite undertaking.

The Panel considered that AstraZeneca had not paid sufficient attention to a number of aspects of the production, certification and use of the leavepiece in question. Although the company had been let down by its agency, which had knowingly provided it with an inaccurate response on one point, its governance of the agency had been extremely poor and AstraZeneca had not undertaken sufficient checks when certifying the material and responding to the complaint. The Panel noted that even a brief perusal of the EMIS website, which it had undertaken on conclusion of this case, revealed the comment that 'Emis web allows you to extract and report on their latest blood pressure reading'. Further, the recent material provided by the complainant indicated, contrary to AstraZeneca's earlier response, that the latest readings could be extracted. This was now not disputed by AstraZeneca.

The Panel noted that AstraZeneca had initially submitted that at the WebEx and teleconference on 20 and 26 May a copy of the leavepiece was shown and certain points were explained verbally. The Panel had raised concerns regarding the lack of any written briefing. However, it subsequently transpired that slides had indeed been shown and then distributed to at least one sales manager. The Panel was concerned

that one slide described Forxiga as 'The metformin ...' and that it was 'to be habitually prescribed as the first choice add-in across the pathway for T2D patients who would benefit from HbA1c control and Weight Loss'. Forxiga was not so licensed. The Panel noted that these claims had not been the subject of complaint. The Panel was also concerned that the final slide stated that each team was to agree how it should be used locally. In the Panel's view this should have come to light in AstraZeneca's enquiries before it responded to a question from the Panel regarding representatives' briefing material. The Panel was concerned that this material had not been before it when it considered the complaint and it was extremely concerned that the material was not certified.

The Panel was also concerned about the certification process in relation to the leavepiece. It was difficult to see how the leavepiece could have been certified unless the signatories had been able to satisfy themselves that when used on the EMIS web system the instructions and output complied with the Code. This had not been done.

The Panel was extremely disappointed by the conduct of AstraZeneca as outlined above. Self-regulation relied, *inter alia*, upon the provision of complete and accurate information to the Panel. It noted the steps undertaken by AstraZeneca to address the issues raised but, nonetheless, considered that the circumstances warranted reporting the company to the Appeal Board under Paragraph 8.2 for it to consider in relation to Paragraphs 11.3 and 11.4 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments above about AstraZeneca's failings with regard to the production, certification and use of the leavepiece in question.

The Appeal Board noted AstraZeneca had limited expertise with regard to the EMIS Web clinical system and in that regard had relied upon its agency which had let it down. Nonetheless the company's failings went way beyond merely relying on the agency's expertise. The company had demonstrated extremely poor governance in this matter. This was not acceptable. The Appeal Board did not understand why representatives had not received a detailed briefing given the complexity of the EMIS system. AstraZeneca had taken full responsibility for its failings and had acted to ensure that such failings did not reoccur. Nonetheless, the Appeal Board considered that it was fundamental for effective self-regulation for companies to provide accurate information to the Panel and for failing to do so and for exercising poor governance it publicly reprimanded AstraZeneca in accordance with Paragraph 11.3 of the Constitution and Procedure.

The Appeal Board noted the Panel's rulings and in particular its view that instructions given in the leavepiece might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. This raised issues of patient safety. This was unacceptable. Consequently the Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution

and Procedure, to require AstraZeneca to issue a corrective statement to all recipients of the leavepiece to clarify the position. [The corrective statement appears at the end of the report].

A clinical pharmacist complained about instructions produced by AstraZeneca UK Limited about how to create an EMIS Web clinical system search to identify patients suitable for treatment with Forxiga (dapagliflozin) (ref 716.131.011).

Forxiga was indicated in adults aged 18 years and older with type 2 diabetes to improve glycaemic control as monotherapy when diet and exercise alone did not provide adequate glycaemic control in patients for whom use of metformin was considered inappropriate due to intolerance. It was also indicated in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, did not provide adequate glycaemic control.

The item was a leavepiece entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. Above this on the front page was a container with a tap releasing sugar. Below the title was a description in smaller bold text of where the prescribing information and adverse event reporting could be found followed by 'FORXIGA is not indicated for weight loss and is not recommended for use in patients with an [eGFR] < 60 mL/min/1.73m². FORXIGA is not licensed for use with thiazolidinedione or GLP-1 agonists'. The leavepiece gave detailed instructions for the search including six search criteria.

COMPLAINT

The complainant alleged that the search instructions were potentially misleading and could easily identify patients who would not be suitable for treatment. The instructions showed how to add criteria for body mass index (BMI), glomerular filtration rate (GFR) and glycosylated haemoglobin (HbA1c). In all cases a clinical code was added with a qualifying value. However, no time restriction was added to qualify these values.

The complainant explained the flaw as follows: patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. However, the value should also be the most recent recorded on the system. This meant a patient with an HbA1c of 48 now who had previously had an HbA1c of 63 should not be included in the final search. However, by applying the instruction as specified they would be included for consideration.

The complainant alleged that whilst he/she hoped that a clinical review would subsequently deem the patient as inappropriate for treatment, the search instructions could be construed as misleading by including such patients. By creating a sub-optimal search the usual high standards demonstrated by the pharmaceutical industry had not been maintained.

The complainant hoped that the instructions would be withdrawn from circulation and, if desired, replaced with some that were more robust and accurate.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2 and 9.1 of the Code.

RESPONSE

AstraZeneca explained that the Forxiga EMIS search instructions included in the leavepiece were intended to be used by health professionals who used the EMIS Web clinical system. The EMIS Web clinical system allowed primary, secondary and community health professionals to view and contribute to a patient's electronic healthcare record.

The Forxiga EMIS search instructions were intended to enable health professionals to identify type 2 diabetics who were uncontrolled and overweight and who might be suitable for Forxiga treatment. The instructions guided the selection of patients with records held in the EMIS Web system which fulfilled the following criteria:

- Patients aged ≥ 18 years and ≤ 75 years

Forxiga was indicated for patients aged 18 years and over. Section 4.4 of the summary of product characteristics (SPC) stated that therapeutic experience in patients 75 years and older was limited and Forxiga was not recommended for patients in this population. Therefore, patients with a recorded age of 18 - 75 were included within the search results.

- Patients identified as having type 2 diabetes

Forxiga was indicated for the treatment of type 2 diabetes. Therefore, patients with a recorded diagnosis of type 2 diabetes were included in the search results.

- Patients not prescribed a loop diuretic in the last 3 months

Forxiga was not recommended for use in patients on loop diuretics (Section 4.4 of the SPC). Therefore, patients with a recorded prescription for a loop diuretic in the last 3 months were excluded from the search results.

- Patients with a body mass index (BMI) of ≥ 25 kg/m²

Treatment with Forxiga was not limited to those who were overweight or those with a particular BMI. However, given its known effect in reducing body weight (Section 5.1 of the SPC) it had the potential to particularly benefit patients in whom weight loss would be valuable. Patients with a BMI > 25 kg/m² were defined as being overweight and as such might benefit from weight loss. Therefore, patients with a record indicating a BMI > 25 kg/m² were included in the search results.

- Patients with glycosylated haemoglobin (HbA1c) ≥ 58 mmol/mol

Forxiga was indicated for patients with type 2 diabetes mellitus to improve glycaemic control. No specific HbA1c values were stated in the SPC. Guidelines indicated that there was no single figure that defined adequate glycaemic control. Rather, HbA1c goals should be individually tailored. The decision as to what HbA1c threshold should trigger the decision to modify a patient's treatment was a matter of clinical judgement tailored to the needs of each patient.

The 58mmol/mol criterion was selected on the basis of the value specified for treatment intensification in the National Institute of Health and Care Excellence's (NICE) Draft Guidelines for the Management of Type 2 Diabetes and was consistent with the value set in the Quality and Outcomes Framework (QOF) diabetes indicators. Therefore, patients with a recorded HbA1c >58mmol/mol were included in the search results.

- Patients with a recorded eGFR \geq 60ml/min/1.73 m²

Forxiga was not recommended for use in patients with moderate to severe renal impairment (patients with CrCl (Creatine clearance) < 60ml/min or eGFR (estimated Glomerular Filtration Rate) < 60ml/min/1.73 m²), (Section 4.4 of the SPC). Therefore, patients with a recorded eGFR value \geq 60 ml/min/1.73 m² were included in the search results.

AstraZeneca submitted that no timeframe was specified for the selection criteria, with the exception of the loop diuretic exclusion. If a timeframe had been specified then patients currently uncontrolled and overweight might not be included in the search results. For example, if a 3 month timeframe had been specified for the HbA1c value then patients with no HbA1c value recorded within the last 3 months, who might potentially still be uncontrolled, would not be included. Not imposing a time restriction also recognised the importance of considering a patient's blood glucose and weight control over time, rather than looking at a single point in time. Importantly, the list generated would include the dates on which measurements were recorded.

Once the search criteria had been built the instructions then continued to describe how to produce the patient list. Health professionals were then to identify patients that might be suitable for Forxiga treatment after further clinical evaluation. Patients appearing on the list might not be suitable for treatment with Forxiga for any number of reasons such as allergy to an ingredient. To further support such clinical decision making the leavepiece provided information on important situations in which Forxiga should not be prescribed. Prescribing information, as well as adverse event information, was also included.

In line with standard UK clinical practice, and as specified in the General Medical Council's Good Medical Practice, AstraZeneca expected doctors and other health professionals to 'prescribe medicines only when they had adequate knowledge of the patient's health and were satisfied that the medicine or treatment served the patient's needs'.

In AstraZeneca's view no health professional would ever prescribe solely on the contents of a computer generated list. Rather, they would always use clinical judgement and consider the patient's current health status when making prescribing decisions.

AstraZeneca stated that the instructions did not suggest that Forxiga was indicated or should be prescribed for all patients that appeared in the search results. Rather, the instructions clearly stated in the title that patients identified '**may** be suitable for treatment with dapagliflozin' (emphasis added). As detailed above the search criteria were designed to reflect the Forxiga SPC, along with values appearing in the NICE guidelines and QOF indicators for type 2 diabetes.

AstraZeneca submitted that Forxiga had been promoted in accordance with particulars in the SPC and denied a breach of Clause 3.2.

AstraZeneca stated that its intention in assembling the list of instructions was to provide health professionals who used the EMIS Web system, a way to generate a list of patients who might be suitable for treatment with Forxiga. AstraZeneca firmly believed that health professionals would not prescribe solely on the basis of a computer generated list but rather would consider individual patient's needs and reach clinically-reasoned prescribing decisions.

As such, AstraZeneca submitted that the leavepiece was not misleading and that Forxiga had been promoted in a transparent manner that encouraged rational prescribing and in accordance with its SPC. Consequently, AstraZeneca denied a breach of Clause 7.2.

AstraZeneca submitted that its intention with this leavepiece, as explained above, was in line with the letter and spirit of the Code. AstraZeneca believed that this would be appreciated by the majority of health professionals who saw the material. High standards had been maintained and AstraZeneca denied a breach of Clause 9.1.

For the reasons detailed above, AstraZeneca also denied a breach of Clause 2.

In conclusion AstraZeneca reiterated that its intention with the leavepiece was to provide a tool to support health professionals who wished to identify patients who might be suitable for treatment with Forxiga. Such a tool could not, and should not, be a substitute for a clinician's professional judgment which would consider the individual patients' needs to fully inform a prescribing decision.

In response to a request for further information AstraZeneca stated that the Diabetes Sales Leadership Team (heads of regional business, regional sales managers, and regional account managers) was briefed on the use of the leavepiece on 20 and 26 May 2015 via a WebEx and teleconference. A copy of the leavepiece was shown and the following points were explained verbally:

- The leavepiece was to be offered to healthcare professionals who had an interest in identifying

their diabetic patients who might be suitable for treatment with Forxiga

- Representatives could only provide the leavepiece and must not be involved in any other way beyond provision of the leavepiece
- The leavepiece was available for representatives to order via the usual internal process.

The leadership team was instructed to cascade this information to their sales teams in their upcoming meetings. Consequently there was no written briefing material.

With regard to the search criteria and screenshot, AstraZeneca submitted that EMISWeb was a clinical system that allowed health professionals to record and use information to support patient care. A component of EMIS Web's functionality was the ability to perform searches and reports from the patient database. Practices would commonly run reports from their clinical system to assist in identifying patients for review.

All six search criteria stated in the leavepiece must be fulfilled in order for a patient's details to appear in the list generated. The report generated was not affected by the order of the search criteria. The example report on page 5 of the leavepiece was included at the end of the step-by-step guide to indicate that a report should now be available for extraction and the report should resemble the example. The example report was generated using dummy patients in a test system. AstraZeneca consulted with the agency that produced the step-by-step guide which confirmed that a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated.

With regard to applying a date range for the search, AstraZeneca stated that the agency that produced the step-by-step instructions confirmed that it was not possible to perform a search for only the latest HbA1c value on the EMIS Web clinical system.

Applying a date range for the search criteria was possible, however as stated previously this had certain limitations. For example, if a 3 month timeframe had been specified for the HbA1c value then patients with a latest HbA1c of 58mmol/mol or greater but not recorded within the last three months would not be included in the report. Also, applying a date range would not prevent patients with an HbA1c of less than 58mmol/mol being included in the report if they had a historical HbA1c of 58mmol/mol or greater also recorded in that timeframe.

Therefore, no date range was specified and patients who had ever had an HbA1c value of greater than or equal to 58mmol/mol and satisfied all the additional criteria would be included in the report even if their most recent HbA1c reading was less than 58mmol/mol. Not imposing a time restriction also recognised the importance of considering a patient's HbA1c over time. The report included the dates on which the measurements were recorded.

AstraZeneca submitted that an example might help to illustrate why the history might be clinically useful:

Patient John Smith had the following HbA1c history:

John Smith	Date	HbA1c (mmol/mol)
	December 2014	62
	June 2014	60
	December 2013	64
	June 2013	67
	December 2012	65

Such a history of hyperglycaemia would appear in the report and might prompt the clinician to undertake a detailed case review. Upon review it might, for example, become apparent that:

- a) the patient had not had a more recent HbA1c value record – they might therefore warrant re-testing and further follow up
- b) There was a more recent HbA1c value of 56mmol/mol available. This might prompt the HCP to carefully evaluate the patient's individual case based on the totality of data and make a clinical decision as to further management.

PANEL RULING

The Panel noted that the leavepiece was entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. The leavepiece then described the EMIS Web search in 9 steps as follows:

- 1 Setup initial search
- 2 Add Age Range to Search
- 3 Add Read Code to Search
- 4 Add Medication to Search
- 5 Add BMI to Search
- 6 Add HbA1c to search
- 7 Add GFR to search
- 8 Save and Run Report
- 9 Build Report Output.

Each step included detailed instructions and some included screenshot examples.

The Panel noted that the complainant was particularly concerned that no time restriction was added to qualify BMI, GFR and HbA1c values which were used as search criteria. In the complainant's view the HbA1c value should be that most recently recorded on the system. The complainant explained that patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. By applying the instruction as specified, a patient with an HbA1c of 48 now who had previously had an HbA1c of 63 would be included for consideration when they should not be and the search instructions could be construed as misleading by including such patients.

The Panel noted the order of the search criteria, age, read code, and medication were followed by BMI before selecting HbA1c and GFR. The report was then run (Step 8). Step 9, Build Report Output, instructed users to add BMI (22K) and value ≥ 25 before adding columns for HbA1c and GFR but unlike BMI no

values were listed for these two criteria at this step in the description in the leavepiece. In the example screenshot of the completed report which appeared below step 9, the column of BMI values was fully populated for each identified patient and appeared before the HbA1c column. Neither the HbA1c nor GFR columns were fully populated. The Panel noted AstraZeneca's submission that the example report was generated using dummy patients in a test system and the agency that produced the step-by-step guide confirmed that a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated. The Panel considered that this was not clear from the leavepiece and was compounded by the screenshot heading 'The completed report should resemble this screenshot'. The Panel accepted AstraZeneca's submission regarding the responsibility of prescribers but considered that it was important that both the instructions and information on the nature and interpretation of the data retrieved was abundantly clear and otherwise complied with the Code. In this regard the Panel was concerned that nowhere in the leavepiece was there any mention of carrying out a clinical review nor was it referred to in the verbal briefing to the diabetes sales leadership team. In the Panel's view, the leavepiece implied that following the 9 step guide would generate a list of uncontrolled patients with a BMI \geq 25 who were suitable for Forxiga. This would include patients who currently had an HbA1c value of less than 58 but who previously had a value of more than 58 being identified as 'uncontrolled'. This impression was compounded by the title '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. In the Panel's view it might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. The Panel considered that the leavepiece was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that Clause 3.2 stated that promotion of a medicine must be in accordance with its marketing authorization and must not be inconsistent with the SPC. The Panel noted its comments above about the identification of patients. Whilst the Panel noted that BMI was relevant to this therapeutic area, the emphasis on BMI in the title, search criteria and the example completed report screenshot which omitted HbA1c values and the failure to refer to the need to carry out a clinical review meant that Forxiga had been promoted for some patients based solely on their weight. Forxiga was not indicated for weight loss. A breach of Clause 3.2 was ruled.

The Panel however did not consider that the instructions were misleading on the narrow point that no time restrictions were included in the search criteria for BMI, GFR and HbA1c as alleged. No breach of Clause 7.2 was ruled.

The Panel considered that the arrangements were such that high standards had not been maintained; a breach of Clause 9.1 was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure; no breach of Clause 2 was ruled.

During its consideration of this case the Panel was concerned that only in response to a question from the Panel did AstraZeneca confirm that the example completed report screenshot did not represent the real-life situation as implied by the leavepiece. In the Panel's view this should have been addressed prior to certification. The Panel was further concerned about the lack of written briefing material and the limited verbal briefing that was to be cascaded by the leadership team to their sales teams. In the absence of any written briefing, the Panel queried whether all sales teams would have received the same message and whether there was a process for ensuring that all sales teams had been briefed on the leavepiece before it became available for order. The Panel requested that AstraZeneca's attention be drawn to these concerns.

The above report was published in December 2015 and subsequently in the February Code of Practice Review 2016. Further information from the complainant was considered as in the addendum below.

CASE AUTH/2793/9/15 – ADDENDUM

FURTHER INFORMATION FROM THE COMPLAINANT FOLLOWING NOTIFICATION OF THE PANEL'S RULING

The complainant did not appeal but queried AstraZeneca's statement that the agency which produced the instructions confirmed that it was not possible to search for only the latest HbA1c. Whilst not disputing the validity of the statement from AstraZeneca, the complainant challenged the overall assertion as being patently false.

The complainant explained that the quality and outcomes framework (QOF) for the GP contract was constructed to check for the most recent values for, *inter alia*, blood pressure and HbA1c so clearly it was possible. Further it was easily possible to construct such searches within EMIS Web and examples were provided.

The complainant's comments were provided to AstraZeneca which was asked for detailed comments.

COMMENTS FROM ASTRAZENECA

AstraZeneca stated that it had commissioned a reputable agency to develop the material in question. Upon receiving the complaint AstraZeneca conducted a full investigation and asked its agency for detailed information. The agency informed AstraZeneca that it was not possible to search for only the latest HbA1c value on the EMIS Web clinical system. Recognising the importance of this point, AstraZeneca sought further explicit confirmation and the agency validated its understanding by contacting an EMIS website user. The agency's response was provided. AstraZeneca stated that it did not have access to the EMIS Web clinical system and thus could not validate the information. AstraZeneca submitted it had provided this information to the PMCPA in good faith.

As per its undertaking, the material in question had been withdrawn. AstraZeneca would no longer use

the agency to produce such material. AstraZeneca would forward the complainant's comments to the agency.

AstraZeneca's comments were sent to the complainant.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that it seemed that the agency engaged by AstraZeneca discussed searches with an EMIS website practice manager. In AstraZeneca's response three points were made about searches, date criteria and limiting reporting to certain values. The complainant submitted that each was false.

- 1 'You can only apply a date range to the search. You cannot ask for only the latest in any of the value criteria'.

The complainant stated it was possible to search on data and to request EMIS to look at only the latest value. It was also possible to look for the earliest value, the highest and the lowest with or without a date restriction. Examples were provided.

- 2 'You can only apply a date range to the report feature. You cannot ask only for the latest value'.

The complainant stated that searches in EMIS identified the patient. Reports allowed the creation of formatted information about the patients within a search group for easier viewing or export. Documents from EMIS about how to create searches and reports were provided. In the document on reports, under the heading 'Create a list report', step 8 mentioned that users could 'use the Feature Builder screen to add the required criteria; this is the same method as adding a rule to a search'. The searches documented under the 'Add a rule' section clearly described how a rule was created and could be restricted to give the latest values, again using the 'latest blood pressure more than 120/80' type of example.

- 3 'In answer to the specific question – it is not possible to ask EMIS Web system to return only the latest value in the output report'.

The complainant interpreted this point as being the same as point 2 above.

The complainant also provided a copy of how to create another search from the EMIS support website that further demonstrated restrictions could be made in reporting the latest values in searches and reports. Additionally there were three screenshots of a clinical system from the QOF searches. The basis of QOF was to pay GPs based on performance. For example, a practice must get a certain proportion of patients with diabetes to an HbA1c controlled value of 59 or less. The criteria for QOF established that the value must be within the year of QOF (so that last 12 months when the search runs for a final time on 31 March and that the most recent value is 59 or lower). The practice would not get paid should the patients have an HbA1c of below 59 at the start of the year but above 59 come the end of the year – so the search looked for the latest value within the year timeframe.

The complainant provided three screenshots showing the search process for a patient with an HbA1c below the target in the last 12 months, one for a patient where the HbA1c was measured but was not at target and the final screenshot was of the actual result – on the same date – for the patient who failed to make the QOF criteria.

The complainant submitted that in summary, limiting a search by date and clinical value was possible within EMIS Web – QOF could not exist without that capability. Those unfamiliar with EMIS Web and GP clinical system might find some of the above difficult to follow and understand but the assertion that searches and reports could not return only the latest results was false.

FURTHER PMCPA CONSIDERATION

Following receipt of the additional information from both parties the Authority decided that the original Panel should reconvene to consider this matter in relation to Paragraph 8 of the Constitution and Procedure. AstraZeneca was so informed, provided with the complainant's further comments and asked to respond.

COMMENTS FROM ASTRAZENECA

AstraZeneca stated that it had recently consulted another agency experienced with EMIS Web, which confirmed that it was possible, using in-built report building functionality, to have the system return information for patients' *latest HbA1c readings*. AstraZeneca therefore acknowledged that, contrary to the information in its original response, the statement made by the complainant was correct.

AstraZeneca and the marketing company president were extremely disappointed and recognised that providing a full and frank disclosure to the PMCPA formed the basis of self-regulation. AstraZeneca conducted a full investigation into the circumstances that led to its failing to provide such a response in this case and was committed to addressing the errors that occurred.

As noted in its first response to the complainant's query, AstraZeneca provided its understanding of the limits of the search functionality in EMIS Web in good faith and considered that it had been badly let down by the agency. In addition, AstraZeneca acknowledged that there had been several failings on its part that contributed to the development of misleading search instructions in the leavepiece and the provision of inaccurate information to the Panel. These failings, and the steps taken to address them, were detailed below.

Development of the leavepiece and first investigation

AstraZeneca initially engaged the services of the agency that generated the search instructions in the leavepiece, in September 2011. Since then AstraZeneca had worked with the agency on many occasions and developed a trusting relationship with a master services agreement in place. Due diligence was conducted in 2011 and, since then, had

been repeated multiple times. Such due diligence had covered, *inter alia*, confidentiality, data privacy, anti-bribery and corruption and good promotional practice. AstraZeneca selected the agency to work on this project (which included instructions for three other clinical systems) as it was considered to have strong technical expertise in the relevant clinical systems and had produced similar materials for another pharmaceutical company. AstraZeneca stated that the agency's proposal was accepted over another from a competing agency based on its overall strength. AstraZeneca was unable to provide this proposal as both AstraZeneca's and the agency's copies were in the possession of employees that had since left the respective organisations.

After an initial scoping meeting, AstraZeneca agreed a project plan for the agency to develop a set of simple, precise and step-wise instructions that would make using general practice clinical systems conduct a review of patients with type 2 diabetes a quick and effective process. It was agreed that instructions for, *inter alia*, the EMIS Web system, would be generated for inclusion in a leavepiece specific to that system. The agency agreed to test the instructions both internally and externally. This testing was to involve assessment from a 'usability and clinical perspective using in-house access to live prescribing systems and long-standing relationships with clinical sites throughout the UK'. AstraZeneca considered it particularly important that the agency conducted thorough testing on its behalf given that it was unable to do so itself; AstraZeneca did not have access to the EMIS Web clinical system or patient data required for comprehensive testing. Also, as noted in the business requirements document, the final report was required to show, *inter alia*, the latest HbA1c result. However, the instructions produced for EMIS Web, unlike the instructions for other systems, did not search on the latest HbA1c result.

After receiving the complaint and during the course of its first investigation, AstraZeneca asked the agency whether it was possible to search for latest values in EMIS Web. The agency responded:

'I have just spoken to an EMIS Web site and asked the specific question around the reporting and search criteria. Here are the responses from the practice manager of this site:

- You can only apply a date range to the search. You cannot ask for only the latest in any of the value criteria
- You can only apply a date range to the report feature. You cannot ask for only the latest value
- In answer to the specific question – it is not possible to ask EMIS Web system to only return the latest value in the report output.'

AstraZeneca took this to mean that it was not possible to conduct a search for the latest HbA1c value.

Second Investigation

In an interview conducted during AstraZeneca's second investigation, the agency stated that this email

relayed the comments of a practice manager, and did not reflect its own understanding of EMIS Web search functionality. The agency did not previously mention this, or correct the information in the email from the practice manager, even though it had now admitted that it knew the information was inaccurate at the time and that a search for the latest HbA1c value was possible.

If the agency, which AstraZeneca contracted as technical experts on the EMIS Web system, had during the first investigation correctly stated that searching for the latest HbA1c value was possible in EMIS Web, AstraZeneca would have put this information into its initial response to the PMCPA. It was absolutely not its intention to provide inaccurate information.

As part of its second investigation AstraZeneca identified two further failings:

- 1 To gain comfort with the technical aspects of the search instructions and aid its review, AstraZeneca asked that the agency to walk it through the search instructions and create a 'plain English' version. This version was referred to as 'process report'. Given that the signatories could not themselves test the instructions, the Works Agreement and Business Requirements Document made clear that the agency was to conduct user testing (internal and external). The agency confirmed in an email of 13 April 2015 that the set of instructions had been tested externally. AstraZeneca placed a high degree of trust in the agency and understood that this testing had taken place in a robust manner.

AstraZeneca had now discovered that the agency subjected the search instructions to testing at only one practice site. Further, AstraZeneca discovered that the focus of the agency's testing was to assess ease of use rather than to verify accuracy. Despite the agency's failure to thoroughly test the instructions, AstraZeneca acknowledged that its signatories had not inquired into the nature and scope of testing performed by the agency. Given the information discovered during the second investigation, the signatories now regretted that they trusted the agency with respect to the search requirements.

- 2 Contrary to the information provided to the Panel in its original response, AstraZeneca had now learned that a slide deck was sent to at least one member of the sales leadership team. As part of its first investigation AstraZeneca interviewed those responsible for creation of the leavepiece, both of whom recalled there not being any form of written briefing document. In its second investigation, AstraZeneca extended interviews to other staff who had worked with the marketing team on this project. A manager produced slides outlining the project for a WebEx on 20 and 26 of May and later emailed these to at least one other manager. The slides had not been certified which was a significant failure to follow the standard operating procedure (SOP) on the Approval of Materials/Activities for Certification and Examination which stated that 'Representative

training materials used to instruct representatives about a medicine or how the product should be promoted' should be certified.

AstraZeneca acknowledged that the circumstances leading up to the approval of the leavepiece were wholly unacceptable, and that its first investigation into this complaint was inadequate. It reiterated its commitment to addressing these issues to ensure that such mistakes were never repeated.

It was never AstraZeneca's intention to provide inaccurate information to the Panel, but this was nonetheless what had happened. The UK marketing company president personally apologised to the Panel for AstraZeneca's conduct. AstraZeneca took full responsibility for the agency's actions as well as of those involved in the development, approval and certification of the leavepiece. The senior management team was fully committed to addressing the contributing factors and improving processes and controls to ensure this did not recur.

Actions taken to ensure such failings do not recur

Since receiving the Panel's ruling, AstraZeneca had taken a number of actions including briefing and training staff. Details were provided.

Conclusion

In summary, AstraZeneca provided its understanding of the limits of the search functionality in EMIS Web in good faith and considered that it had been badly let down by the agency that confirmed this understanding. AstraZeneca acknowledged that there had been several failings on its part; one with certification that contributed to the development of the misleading search instructions in the leavepiece and subsequently one with the initial investigation that led to the provision of inaccurate information to the Panel.

AstraZeneca had a robust compliance framework to help prevent, detect and respond to risks and incidents effectively. This framework included, *inter alia*, elements relating to monitoring, training, standard setting, risk identification and assessment and reporting. It would be happy to provide additional information regarding its comprehensive compliance programme to demonstrate its commitment to ensuring issues like this did not recur.

FURTHER CONSIDERATION BY THE PANEL

The Panel noted that it was considering this matter in relation to Paragraph 8.2 of the Constitution and Procedure which provided that the Panel might report to the Appeal Board any company whose conduct in relation to the Code, or in relation to a particular case before it, or because it repeatedly breached the Code such that it raised concerns about the company's procedures, warranted consideration by the Appeal Board. Such a report to the Appeal Board might be made notwithstanding the fact that a company had provided an undertaking requested by the Panel. The Panel noted that AstraZeneca had provided the requisite undertaking.

The Panel noted its rulings of breaches of Clauses 7.2 and 3.2 and no breach of Clauses 2 and 7.2. It noted that in deciding whether to report a company under Paragraph 8.2 of the Constitution and Procedure it was not limited to matters which were before the Panel during its consideration of a case.

The Panel considered that AstraZeneca had not paid sufficient attention to a number of aspects of the production, certification and use of the leavepiece in question. Although the company had been let down by its agency, which had knowingly provided it with an inaccurate response on one point, its governance of the agency had been extremely poor and AstraZeneca had not undertaken sufficient checks when certifying the material and when responding to the complaint. The Panel noted that even a brief perusal of the EMIS website, which it had undertaken on conclusion of this case, revealed the comment that 'Emis web allows you to extract and report on their latest blood pressure reading'. Further, the recent material provided by the complainant indicated, contrary to AstraZeneca's earlier response, that the latest readings could be extracted. This was now not disputed by AstraZeneca.

The Panel noted that AstraZeneca had initially submitted that at the WebEx and teleconference on 20 and 26 May a copy of the leavepiece was shown and certain points were explained verbally. The Panel had raised concerns regarding the lack of any written briefing. However, it had subsequently transpired that slides had indeed been shown and then distributed to at least one sales manager. The Panel was concerned that the second slide described Forxiga as 'The metformin ...' and that it was 'to be habitually prescribed as the first choice add-in across the pathway for T2D patients who would benefit from HbA1c control and Weight Loss'. Forxiga was not so licensed. The Panel noted that these claims had not been the subject of complaint. The Panel was also concerned that the final slide stated that each team was to agree how it should be used locally. In the Panel's view this should have come to light in AstraZeneca's enquiries before it responded to a question from the Panel regarding representatives' briefing material. The Panel was concerned that this material had not been before the Panel when it considered the complaint. In addition, the Panel was extremely concerned that the material was not certified. It was not clear why the material had not been certified.

The Panel was also concerned about the certification process in relation to the leavepiece in question. It was difficult to see how the material could have been certified unless the signatories had been able to satisfy themselves that when used on the EMIS web system the instructions and output complied with the Code. This had not been done. According to AstraZeneca, testing by its agency was to include in-house access to live prescribing systems. It was unclear why AstraZeneca considered it could not, at the very least, be present during in-house testing to question the agency which could be done without AstraZeneca having sight or access to the actual prescribing system. AstraZeneca subsequently confirmed that the agency had tested the material externally. It was thus unclear whether

in-house testing had ever taken place. AstraZeneca acknowledged its failure to inquire into the nature and scope of the agency's testing. The Panel considered that, in addition, AstraZeneca had not adequately instructed the agency in this regard at the outset so as to ensure such testing went beyond ease of access.

The Panel noted the due diligence summary provided by AstraZeneca and the issues raised therein.

The Panel was extremely disappointed by AstraZeneca's conduct as outlined above. Self-regulation relied, *inter alia*, upon the provision of complete and accurate information to the Panel. It noted the steps undertaken by AstraZeneca to address some of the issues raised but, nonetheless, considered that the circumstances warranted reporting the company to the Appeal Board under Paragraph 8.2 for it to consider the matter in relation to Paragraphs 11.3 and 11.4 of the Constitution and Procedure.

COMMENTS FROM ASTRAZENECA ON THE REPORT

At the consideration of the report AstraZeneca submitted that it took full responsibility for the failings in this case and was fully committed to addressing them. It acknowledged that this was a very serious matter. AstraZeneca had already implemented a number of actions to prevent this happening again. Further actions and resource were being implemented to support this. These actions had the full support of the senior leaders both in the UK marketing company and at a global level. AstraZeneca was committed to continual improvement of compliance activities and standards. 'We do the right thing' was one of the company's five core values.

Completed activities included: staff briefed on details of this case at Quarterly Code Review; enhanced due diligence on third party vendors regarding familiarity with the Code and its requirements; suspension of all work with the agency involved and notice to terminate given; trained signatories and originators on failings in this case; updated local working structure on handling Code of Practice complaints; revised approval SOP to be more explicit regarding briefing documents and ensure signatories had all the required information.

Planned activities included: refresher training with signatory revalidation programme to be introduced; third party job bag audits; active review of the current approval system with the goal of replacing it; training for all brand teams on regulatory obligations and responsibilities, properly briefing and managing agencies and support materials and where to seek help; training to new brand team members as part of induction programme; annual refresh training for all marketing staff (as part of wider programme); develop an agency handbook to explain AstraZeneca's expectations; Compliance Assurance Task Force established with a wide ranging remit, initiated by country president, led by the medical director with cross functional representation; 'Right Thing Right Way' initiative; further dedicated resource to support compliance to include a compliance training manager and SOP co-ordinator.

APPEAL BOARD CONSIDERATION

The Appeal Board noted the Panel's rulings and comments about AstraZeneca's failings with regard to the production, certification and use of the leavepiece in question.

The Appeal Board noted AstraZeneca had limited expertise with regard to the EMIS Web clinical system and relied upon the knowledge of its agency which had let it down. Nonetheless the company's failings went beyond merely relying on the agency's expertise. In the Appeal Board's view the company had demonstrated extremely poor governance in this matter. This was not acceptable. The Appeal Board did not understand why representatives had not received a detailed briefing given the complexity of the EMIS system. The Appeal Board noted that AstraZeneca had taken full responsibility for its failings in this case and had already undertaken, or was due to undertake, a number of measures to ensure that such failings did not reoccur. Nonetheless, the Appeal Board considered that it was fundamental for effective self-regulation for companies to provide accurate information to the Panel and for failing to do so and for exercising poor governance it publicly reprimanded AstraZeneca in accordance with Paragraph 11.3 of the Constitution and Procedure.

The Appeal Board noted the Panel's rulings and in particular its view that instructions given in the leavepiece might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. This raised issues of patient safety. This was unacceptable. Consequently the Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require AstraZeneca to issue a corrective statement to all recipients of the leavepiece to clarify the position. The corrective statement should refer to the case report. Under Paragraph 11.3 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].

Complaint received	10 September 2015
Undertaking received	16 November 2015
Appeal Board consideration	7 March 2016
Panel reconvened	24 February 2016
Corrective statement issued	15 June 2016
Case completed	17 March 2016
Updated case report including addendum published	15 June 2016

On 15 June 2016, AstraZeneca sent the following corrective statement to recipients of the leavepiece at issue.

'Dear Healthcare Professional,

Corrective Statement

Case AUTH/2793/9/15: Identifying patients suitable for Forxiga treatment

I am writing to you as I understand that your Practice uses the EMIS Web Clinical System.

AstraZeneca produced a leavepiece entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions' (ref 716.131.011). AstraZeneca markets Forxiga®▼ (dapagliflozin) which is indicated to improve glycaemic control in certain type 2 diabetic patients. You may have been provided with a copy of the leavepiece sometime between 19 May 2015 and 13 November 2015.

Following a complaint under the Association of the British Pharmaceutical Industry (ABPI) Code of Practice for the Pharmaceutical Industry, the Code of Practice Panel ruled that the leavepiece was misleading, it was inconsistent with the Forxiga summary of product characteristics as

following the 9 step guide could lead to patients being identified as suitable for Forxiga treatment based solely on their weight and not on HbA1c levels. Forxiga is not indicated for weight loss. The Panel considered that high standards had not been maintained. Subsequently the complainant brought to light that AstraZeneca had provided inaccurate information. As a result of this and other governance issues that subsequently emerged, the Panel reported AstraZeneca to the Code of Practice Appeal Board. The Appeal Board was concerned that use of the leavepiece might lead to the inappropriate prescription of Forxiga, and it considered that it was important that recipients of the leavepiece should be made aware of this. As a result AstraZeneca has been required to issue this corrective statement and to refer to the published report for the case which contains full details.

AstraZeneca takes its responsibilities under the ABPI Code seriously and is disappointed at these failings. As an organisation we will take all steps needed to ensure this is not repeated.

Best regards,'

ANONYMOUS, NON-CONTACTABLE NHS WHISTLEBLOWER v NAPP

Promotion of Remsima

An anonymous, non-contactable 'NHS whistleblower' complained about the promotion of Remsima (infliximab) by Napp Pharmaceuticals at a two day meeting for UK health professionals held in Norway. Also at issue was a Remsima leavepiece which advocated switching from Remicade to Remsima. Remsima was a biosimilar of Remicade (marketed by Merck Sharp & Dohme) and both were anti-tumour necrosis factor (anti-TNF) medicines and could be used in the treatment of psoriasis, Crohn's disease and ulcerative colitis.

The meeting held in Norway was entitled 'Norway IBD [inflammatory bowel disease] exchange'. The complainant stated that he/she was extremely concerned that two colleagues who were implementing a wholesale switch of their patients to the new medicine, had been invited by Napp to a four day 'scientific meeting' in Norway. Seemingly as a reward for switching patients to Remsima. Given recent newspaper headlines about pharmaceutical companies taking NHS decision makers overseas on junkets, it begged belief that this activity was still so blatantly pursued by the UK pharmaceutical industry.

The complainant summarised his/her complaint by stating that this type of activity did nothing for the reputation of either Napp or the UK pharmaceutical industry as a whole. More worrying was the effect that this negligent and unethical behaviour would have on patients. [This comment was taken by the Panel to apply equally to the meeting and the leavepiece.]

The detailed response from Napp is given below.

The Panel noted that the agenda for the meeting stated that the focus of the event was to share best practice in the treatment of IBD in both the UK and Norway, to facilitate discussion about the standard of care in Norway compared with the UK and to identify areas of best practice in both countries. It was further stated that discussions would also focus on the introduction of biosimilars for the treatment of IBD including clinician and patient experience in Norway. The front cover of the agenda stated 'This meeting is organised by Napp Pharmaceuticals. Discussion of Napp Pharmaceuticals' products will take place at this event'. Prescribing information for Remsima was included.

The meeting had been developed in response to feed-back from pre-launch advisory boards that real world evidence and experience from clinicians who had used Remsima was important. Remsima had been available in Norway since January 2014 but not launched in the UK until February 2015. Biosimilar infliximab in Norway had a 63% market share. One of the stated aims of the meeting was to allow key

opinion leaders to share real world experience with Norwegian clinicians who used Remsima in IBD given that clinical data in IBD patients and practical experience in the UK of using biosimilar infliximab was very limited. In the Panel's view the meeting was organised specifically with a focus on Remsima and to promote switching from Remicade to Remsima in IBD.

In the Panel's view, the sales force briefing about the meeting, which listed the criteria for inviting potential delegates, further emphasised the importance of Remsima to the meeting for Napp as opposed to sharing best practice as stated on the agenda. The potential delegates appeared to have been chosen for their ability to influence decisions about the use of Remsima.

The Panel noted that the meeting agenda included tours of the gastroenterology clinics of two local university hospitals. Napp had submitted that such tours were so that delegates could see how the biosimilar infliximab was delivered in a real-life clinical setting and speak to clinicians and specialist nurses at the hospitals who had actually administered the product. The Panel noted from the leavepiece at issue below however, that in terms of switching from Remicade to Remsima, it was claimed, *inter alia*, that 'Your clinic won't need to change how it does things' and that there was 'no need for new staff training'. In the Panel's view, although the UK delegates would have a professional interest in seeing the Norwegian clinics, such tours were not integral to the main focus of the meeting. In the agenda given to delegates both hospital tours appeared to be identical in that both would include an overview of the clinic, standards of care and best practice with anti-TNF therapy, patient flow through the system, consultations, infusion procedure, capacity planning and the efficient running of clinics. In the briefing given to the chair and co-chair of the meeting, each of whom would host one of the hospital tours, less detail was given in that it was stated that during the tours it would be 'good if some of the clinic nurses are available, to hear their perspective and views on such things as the infusion procedure, capacity planning, and information that is given to patients to support them'. Overall the Panel considered that it would have made much more logistical sense to have the two Norwegian clinical experts visit the UK to discuss their experiences and relevant patient case histories with their UK counterparts. Alternatively, the Panel queried whether the meeting could have been conducted on-line. It appeared that the two hospital tours had been included to help justify the meeting being held in Norway. Given the lack of a clear and cogent reason to hold the meeting outside the UK, the Panel ruled a breach of the Code.

The Panel noted that the delegates had been invited to a two day meeting in Norway, the primary objective of which appeared to be to allay their concerns about switching IBD patients from Remicade to Remsima. The average total cost of hospitality, to include air fares, was £799.73 per person. The Panel considered that in and of itself, the hospitality had not been excessive although two evening meals each of just over £61 per head was on the limits of acceptability bearing in mind the relevant requirements of the Norwegian Code. Nonetheless, the Panel considered that hosting UK delegates for a two day promotional meeting in Norway, in circumstances where the Panel did not consider that there was a clear and cogent reason for holding the meeting outside the UK, was an inducement to prescribe or recommend Remsima. A breach of the Code was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted that the supplementary information to Clause 2 stated that, *inter alia*, an inducement to prescribe was likely to be in breach of Clause 2. The Panel noted its comments above and considered that holding the meeting in Norway was such as to bring discredit upon and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Upon appeal by Napp, the Appeal Board noted its submission that Remsima was the world's first monoclonal antibody biosimilar of infliximab and that the process by which biosimilars were granted a marketing authorization meant that health professionals were confused and lacked confidence about using them. Napp submitted that there was a significant and legitimate educational need relating to the clinical use of biosimilar infliximab in the UK. The evidence required for Remsima's licence was to show that it and the reference medicine (Remicade) were essentially the same biological substance and clinical studies were only confirmatory. Napp submitted that in the case of infliximab the clinical studies were not in gastroenterology but that extrapolation from rheumatology studies to IBD was possible based on the overall evidence of comparability. Thus there was less direct data on the clinical efficacy and safety of Remsima in gastroenterology than would have been available for Remicade. When Remsima was launched in the UK (February 2015), clinical data in IBD and practical clinical experience with biosimilar infliximab was extremely limited. The Appeal Board further noted Napp's submission that Norwegian clinics, however, had used Remsima since early 2014; the position by June 2015 was that Remsima was used for all new IBD patients nationally and several IBD centres had switched to 100% Remsima.

The Appeal Board noted that apart from the originator medicine, Remicade, which had been on the UK market for 15 years, there were now two biosimilar infliximabs available, Remsima and Inflectra. The Appeal Board noted Napp's submission that planning for the October meeting had started in June when only one or two UK centres were using Remsima. In

that regard, however, the Appeal Board noted that a National Institute for Health and Care Excellence report, 'Introducing biosimilar versions of infliximab: Inflectra and Remsima', published 31 July 2015 and provided by Napp, stated that between April and June 2015 one UK hospital had switched 150 IBD patients from Remicade to Inflectra. The Appeal Board thus noted that shortly after starting to plan the meeting in question, there was published data which referred to relevant experience of switching gastroenterology patients to biosimilar infliximab in the UK, albeit short-term data compared with the longer term use of a biosimilar infliximab in Norway.

The Appeal Board noted that the meeting delegates had toured the two Norwegian hospitals in groups. The tours of the two hospitals lasted in total 3.5 hours. In the newer hospital the group size was ten with smaller groups touring the older hospital. In that regard the Appeal Board queried whether the group sizes and the relatively short time spent in each hospital were compatible with the delegates being able to observe and absorb meaningful, relevant details about service provision, patient flow, logistics etc.

In the Appeal Board's view, given the evidence required for Remsima's marketing authorization that there was no difference in the use, dose or preparation of Remicade and Remsima, and there was UK experience of switching IBD patients from Remicade to a biosimilar infliximab, there was no clear and cogent reason for the UK delegates to travel to Norway for the meeting. That was not to say that some way could not have been found of incorporating the Norwegian experience into a meeting held in the UK. Nonetheless, the Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on that point was unsuccessful.

The Appeal Board noted that UK delegates had attended a two day meeting in Norway, which had been paid for by Napp. The Appeal Board considered that although the level of subsistence had not been excessive, hosting UK delegates for the two day promotional meeting in Norway, where there was no clear and cogent reason for holding that meeting outside the UK, was an inducement to prescribe or recommend Remsima. The Appeal Board thus upheld the Panel's ruling of a breach of the Code. The appeal on that point was unsuccessful.

The Appeal Board noted its rulings above and considered that high standards had not been maintained and it upheld the Panel's ruling of a breach of the Code. The appeal on that point was unsuccessful.

The Appeal Board noted that biosimilars were emerging therapies the regulatory process for which meant that, as with Remsima, direct clinical data might not be available in all therapy areas. Health professionals in therapy areas where the direct clinical data might be lacking needed to understand and have confidence in that process. In that regard the Appeal Board considered that whilst the location of the meeting was unacceptable, the aim of the meeting was not unreasonable. The Appeal Board noted its

rulings and comments above and decided that on the facts of this case, a ruling of a breach of Clause 2 would be disproportionate. On balance, the Appeal Board ruled no breach of Clause 2. The appeal on that point was successful.

The complainant provided a copy of a leavepiece entitled 'Your guide to changing treatment Remicade → Remsima' which explained the process for switching treatments. The complainant was concerned that the industry continued to pursue such an aggressive stance on switching between treatments with little concern for patients, or patient safety. There was no reference in the leavepiece to the conditions which either medicine was used to treat and it was even suggested that there should be no safety concerns associated with switching to Remsima, despite being a recently licensed medicine with limited safety information. The complainant submitted that this type of irresponsible action by the industry put patient's safety, and indeed lives, at risk.

The Panel noted that the leavepiece was a guide to changing treatment from Remicade to Remsima. The leavepiece explained that Remsima was a biosimilar of Remicade. It was stated that patients currently on Remicade could therefore be changed to Remsima treatment providing they were eligible. In that regard the Panel did not consider that it necessarily had to be stated in the main body of the leavepiece which conditions patients would be treated for; in any event, the prescribing information listed the licensed indications for Remsima. The Panel noted that the leavepiece listed those patients who would not be eligible for Remsima treatment (eg those who had discontinued Remicade therapy due to intolerance or lack of efficacy) and those who would be eligible (ie those who currently responded well to or remained stable on Remicade). In addition it was stated that any switch should always be done on a case-by-case basis. Having listed which patients might or might not be eligible for a switch, the leavepiece described how the switch should be carried out and what to expect after switching. On the back of the leavepiece was a highlighted box of text with additional safety information about the risk of tuberculosis during and after treatment with [Remsima].

The Panel did not consider that the leavepiece suggested that there were no safety concerns with Remsima as alleged. The Panel considered that on the basis of the information before it, there was nothing to show that the leavepiece had not encouraged the rational use of the medicine; the eligibility or otherwise of patients had been made clear. The Panel did not consider that the information in the leavepiece was misleading. No breaches of the Code were ruled.

The Panel noted its rulings above and did not consider that high standards had not been maintained. No breach of the Code was ruled. Given its rulings above, the Panel also ruled no breach of Clause 2.

An anonymous, non-contactable complainant who described him/herself as an 'NHS whistleblower' complained about the promotion of Remsima (infliximab) by Napp Pharmaceuticals Limited. At issue

was a two day meeting for UK health professionals held in Norway and a Remsima leavepiece (ref UK/REMS-15078) which advocated switching from Remicade to Remsima. Remsima was a biosimilar of Remicade (marketed by Merck Sharp & Dohme). Both Remsima and Remicade were anti-tumour necrosis factor (anti-TNF) medicines and could be used in the treatment of psoriasis, Crohn's disease and ulcerative colitis.

A Meeting held in Norway, 11-13 October 2015

The meeting was entitled 'Norway IBD [inflammatory bowel disease] exchange'.

COMPLAINT

The complainant stated that he/she was extremely concerned to discover that two colleagues in a named hospital who were implementing a wholesale switch of their patients to the new medicine, had been invited by Napp to a four day 'scientific meeting' in Norway in November. This 'meeting' seemed to be to reward those who were switching to using Remsima which the complainant described as a new version of infliximab. Given recent headlines in The Telegraph about pharmaceutical companies taking NHS decision makers overseas on junkets, it beggared belief that this activity was still so blatantly pursued by the UK pharmaceutical industry.

The complainant summarised his/her complaint by stating that this type of activity did nothing for the reputation of either Napp or the UK pharmaceutical industry as a whole. More worrying was the effect that this negligent and unethical behaviour would have on patients. [This comment was taken by the Panel to apply equally to the meeting and the leavepiece at issue at Point B below.]

When notified of the complaint, Napp was asked to respond in relation to Clauses 2, 9.1, 18.1 and 22 of the Code.

RESPONSE

Napp explained what a biological medicine was and stated that NHS England's recent publication, 'What is a Biosimilar Medicine?', defined a biosimilar medicine as:

'a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy.'

Napp submitted that health professionals, patients and the public often misunderstood what a biosimilar was. Biosimilars were large, complex proteins up to one thousand times larger than small chemical molecules eg aspirin. In contrast to generic versions of small molecules all biological medicines including biosimilars were manufactured within living cells, and so no two batches were ever identical. Instead the regulators accepted a reference range of batch-to-batch variation through a comparability exercise. Napp referred to the European Generic and Biosimilar

Medicines Association brief internet video on 'Biosimilar Medicines: An Opportunity for Healthcare'. The guideline from the European Medicines Agency (EMA) on biosimilars stated that a biosimilar had to demonstrate such comparability by head-to-head, state-of-the-art, physico-chemical analysis; biological testing, and limited clinical trials such that there were no clinically meaningful differences to the originator.

It followed that the originator monoclonal antibody infliximab (Remicade) had many 'versions' over the 15 years since it was first licensed as a result of batch-to-batch variation and manufacturing changes. 'Virtually all monoclonal antibodies have been subject to several changes after authorization – a fact that is not well known by clinicians and that is rarely explicitly communicated'. (Schneider 2013).

The confusion by health professionals about the comparability of biosimilars with the originators had arisen from statements like 'similar but not the same', a problem which had been highlighted by several expert European regulators. An expert rheumatologist wrote:

'Similar but not the same – comparability

There was extensive experience in comparability studies that controlled the safety and efficacy of biologicals after manufacturing changes. Current methods to analyse physicochemical and structural differences were extremely sensitive. Analysis of manufacturing batches of the originator (reference) products had revealed differences after a change in the manufacturing process between the pre- and post-change batches. In these cases, no clinical studies were performed. These differences were similar to those that had raised a lot of concerns when observed between a biosimilar and its reference product. Thus, the slogan "Similar but not the same" applied to originator products at the time of licensing and today!" (Kurti 2014).

Napp submitted that Remsima was the world's first monoclonal antibody biosimilar of infliximab approved by the EMA in July 2013, though 12 biosimilars had been approved in Europe over the past 10 years. Remsima was infliximab just as much as the many batches of originator Remicade were infliximab, and was described as such within the summary of product characteristics (SPC) as Remsima (infliximab). The EMA stated that Remsima was highly similar to the originator and had not shown any clinically meaningful differences as part of its submission.

Napp submitted that the complainant was thus mistaken to describe Remsima as a new version of infliximab. Remsima was no more a new version than were the multiple batches of Remicade. Remicade patients over the past 15 years had effectively received several 'versions' of infliximab – though all falling within a tightly controlled and acceptable reference range.

With regard to the meeting at issue, Napp confirmed that a two day meeting would take place in Oslo from arrival on Sunday afternoon 11 October 2015, to departures after lunch on Tuesday, 13 October (a copy of the agenda was provided). Napp stated that it interpreted 'scientific meeting' as used by

the complainant as a means to draw attention to an ironic or inaccurate use, in this case a junket rather than a truly scientific and educational meeting. Napp submitted that the agenda and the speaker briefings showed that the meeting had an extremely high scientific and educational content. The meeting had been certified as a promotional meeting which was not solely focused on switching between infliximab brands. Napp firmly believed that high standards had been maintained at all times and noted that it had applied the question given in the supplementary information to Clause 22, 'would you and your company be willing to have these arrangements generally known?'. The following approval documents were provided:

- The certified Napp organised Meeting/ Accommodation and Internal Hospitality Proposal Form (ref UK/INM-14009(1)). This detailed the type of meeting, including meeting aims, justification, the agenda, dining arrangements, hotel details, subsistence costs and travel arrangements. Napp noted that dinner costs in the proposal form had been approved as £65/head on Sunday and £70/head on Monday. These were finalised and confirmed as £61.26 and £61.64, respectively. [This form also referred to a similar meeting held in March 2015]
- The certified Napp customer invitation brochure (ref UK/INM-14009(1)a). The front page made it clear that this was a promotional meeting as prominently highlighted by the words: 'This meeting is organised by Napp Pharmaceuticals Limited. Discussion of Napp Pharmaceuticals' products will take place at this event'. The inside of the invitation described the faculty members and the focus of the meeting as well as the agenda. The next page provided contact details and introduced the Napp team. The final page contained the Remsima prescribing information
- The certified Napp internal briefing document which explained the delegate selection criteria (ref UK/INM-14009(1)b). The delegates from each region of the UK, were hospital health professionals (doctors with an interest in gastroenterology medicine or specialist inflammatory bowel disease (IBD) nurses) who cared for patients with IBD, ulcerative colitis or Crohn's disease – both licensed indications for infliximab
- The certified Napp internal speaker agreement proposal form which provided detailed explanations of the agenda, the aims of the meeting and full speaker briefings and biographies for the faculty (ref UK/INM-14009(1)c). The slide sets were currently undergoing review by Napp prior to final certification
- Napp also provided pictures of the conference facilities at the hotel and a spreadsheet detailing all final costs associated with subsistence, accommodation and travel.

Napp stated that it could be seen that that the delegates were not selected based on any form of 'reward' to those switching to Remsima (ref UK/INM-14009(1)b). Each representative could invite up to 3 delegates for a maximum of 20 available places. Twenty seven delegates could be invited and then head office medical and marketing teams decided on the final 20 based upon the documented selection criteria.

Napp noted that the final delegate number was 21.

A list of the invitees and their organisations/hospitals was provided. Of the 21 delegates, only 1 invitee (a specialist nurse) had begun switching and 2 were considering switching. Thus 95% of the delegates (20/21) had not switched IBD patients to Remsima contrary to the complainant's allegation.

The purpose of the promotional meeting was fully described in the 'type of meeting' section of the Napp speaker agreement proposal form (ref UK/INM-14009(1)c). The meeting was not developed to focus primarily on switching patients to Remsima but was in response to feedback from pre-launch key opinion leader advisory boards that sharing real world evidence and experience from clinicians who had used Remsima was important. As described in the background section above, the regulatory process for biosimilars focussed heavily on comparability exercises to demonstrate that the biosimilar was highly similar to the original, and clinical studies were only confirmatory. In the case of biosimilar infliximab, the clinical studies conducted under this pathway included patients with rheumatoid arthritis and ankylosing spondylitis only. Extrapolation to IBD was possible based on the overall evidence of comparability provided from the comparability exercise and due to the conserved pathological mechanism across the diseases. However, this meant that when the medicine was launched in the UK, clinical data in IBD patients and practical clinical experience with biosimilar infliximab was extremely limited. The meeting was held in Norway because it was one of the first European countries to have access to Remsima. Norwegian clinicians began treating patients with Remsima in early 2014, one year before its availability (February 2015) in the UK due to differences in patent expiry dates. Norwegian gastroenterologists had since gained significant practical clinical experience in both new and switched IBD patients. One question could be why the Norway experts could not visit UK to share their insights and experience.

The programme had been designed such that UK delegates could see how biosimilar infliximab was delivered in a real-life clinical setting and speak to clinicians and specialist nurses at the hospitals who had actually administered the product. Furthermore, Napp hoped that by exposing UK health professionals to how IBD was managed in Norway, patient care in the UK would be enhanced. Napp stated that there were visits to two hospitals to experience at first hand the gastroenterology facilities and infusion clinics where infliximab was delivered. Both of these hospitals were key centres for the treatment of IBD in Norway and the two Norwegian professionals who hosted the hospital tours were international key opinion leaders in the field of IBD. There were also meetings with clinic staff and sharing of clinical methods and patient management in a different healthcare setting.

In summary, Napp had organised the promotional Norway IBD exchange to:

- Share real world experience of using Remsima to treat IBD patients in Norway
- Share best treatment practice of IBD in the UK and Norway

- Facilitate learning of IBD treatment in Norway by visiting two key clinical centres of excellence in Oslo
- Facilitate discussions about the standards of care in Norway compared with the UK to identify areas of best practice in both countries.

In view of the information provided, Napp refuted any breach of Clause 18.1, as there had been no gift, pecuniary advantage or benefit offered connected to the promotion of Remsima or as an inducement to prescribe. The meeting arrangements and hospitality were fully aligned to all aspects of Clause 22 and Napp refuted a breach of this clause. Napp had maintained high standards at all times by ensuring the meeting arrangements met all aspects of the Code; it had not brought discredit upon, or reduced confidence in the pharmaceutical industry. Napp denied breaches of Clauses 9.1 and 2.

In response to a request for further information Napp stated that the meeting was promotional; the delegates did not attend as consultants to Napp therefore they were not remunerated and no contractual agreements were put in place. The meeting joining instructions which were sent to delegates prior to the event were provided.

All slide sets used at the meeting were provided as well as feedback from the March and October IBD exchange meetings. Napp submitted that the agendas for the March and October meetings were not identical but were very similar. Details were provided of three amendments made to the October agenda as a result of feedback from the March meeting.

Napp stated that once registration was opened for the October meeting, a much higher proportion of specialist nurses applied to attend than had applied to attend the March meeting. In order to maintain relevance to the audience, an IBD nurse specialist from one of the Norwegian hospitals was included as an additional faculty member. The nurse specialist did not present a distinct session and the agenda was not modified; she was instead asked to contribute her clinical experience to the existing planned sessions and on one of the hospital tours. The agenda for the March meeting was provided. The speakers were essentially the same. Sixteen delegates attended the March meeting; fourteen consultant gastroenterologists and two IBD specialist nurses.

Napp submitted that there had been no particular follow up with any of the delegates of the March or October meetings by Napp head office staff. Napp promotional staff had not been specifically asked to follow up with attendees although it was likely that some or all of the delegates would have met Napp promotional staff as part of routine promotional activities since the meetings occurred but any activity of this type had not been recorded or audited over and above routine promotional call recording.

Napp submitted that two of the delegates had been contracted to provide services to Napp since attending the March exchange meeting; one had attended an advisory board regarding biosimilar infliximab uptake in London in July 2015 and the other authored a Remsima promotional advertorial which was

published in a journal and attended an advisory board regarding biosimilar infliximab uptake in London in July 2015. None of the delegates from the October meeting had provided services to Napp yet since returning from the meeting although two might do so in the near future; there was provisional plans for both to speak at a Napp promotional meeting. A list of the March and October delegates with the above delegates highlighted was provided.

Napp submitted that it routinely monitored Remsima sales to UK hospitals. No additional methods to monitor Remsima use had been implemented in hospitals where Norway exchange meeting delegates were employed. Neither had any exercise been undertaken to specifically correlate sales data against hospitals where Norway exchange meeting delegates were employed.

Napp submitted that in the planning and certification of the meeting arrangements the most recent 2014-2015 Norwegian 'Rules for Marketing of Medicinal Products' was taken into consideration (copy provided). Point 9.04 of this guidance outlined acceptable costs for meetings and stated that 'As a general rule, it shall not exceed what healthcare professionals would have paid if they were to pay it themselves'. There was also specific guidance on the rates that must be adhered to for lunch and dinner under Section 9.04A. This stated that the currently established dinner and lunch rates per person that shall not be exceeded were NOK 822 (£63.22) for dinner and NOK 172 (£13.23) for lunch.

Napp submitted that two dinners were organised during the meeting. The total cost for dinner on Sunday, 11 October at the conference hotel was £4,244.67, which consisted of 27 three course meals at £44.97 each, and four snacks for late arrivals at £7.61 each. The total cost of dinner at a restaurant on Monday, 12 October was £1,620.71 for 30 people including Napp staff and delegates. The cost per head was therefore £54.06. Unfortunately one delegate had to leave unexpectedly at the end of the first day hence only 30 heads for dinner. Receipts for these two dinners were provided. Two lunches were organised; one on Monday, 12 October and the other on Tuesday, 13 October. Both took place at the conference hotel and were part of the day delegate rate charged by the hotel that included room hire; technical equipment and AV hire; support from the hotel staff with AV throughout the meeting; water, tea and coffee refreshments at the break; and hotel pen and paper. A limit was set for the lunch provision by the hotel of £13.23. Relevant correspondence from the hotel was provided. The receipt from the hotel outlined the total cost of 60 day delegate rates for 30 delegates including Napp staff for 2 days as £3,345.56. The cost per head, per day was therefore £55.76 of which the lunch subsistence was £13.23.

Napp submitted that the meeting formally concluded at 13:15 on Tuesday, 13 October, lunch was arranged at the hotel until 14:00. All but two delegates departed by 17:15 or earlier on that day; one delegate departed at 18:40 in order to return to a different UK airport and another departed at 21:25 for personal reasons; Napp did not consider it unreasonable. A table of the delegates' return flights was provided.

Napp confirmed that the two hospital tours undertaken during the visit were to different hospitals and the transfer times were therefore different. On Monday, 12 October the group toured Akershus University Hospital. The transfer time from the hotel was approximately 30 minutes. The tour itself lasted 60 minutes, followed by a 30 minute discussion. There was then a 30 minute transfer back to the hotel. On Tuesday, 13 October the group toured Oslo University Hospital. The transfer time from the hotel was approximately 15 minutes. The tour lasted 90 minutes followed by a 30 minute discussion and a 15 minute transfer back to the hotel.

Napp submitted that Remsima and Inflectra were both the biosimilar infliximab manufactured by Celltrion in South Korea. Inflectra was sold worldwide by Hospira, which was recently acquired by Pfizer. Both Remsima and Inflectra received centralised EU marketing authorizations in September 2013 meaning the product was simultaneously authorised for sale in all European Economic area countries. However, the product was not able to launch immediately in any European territory due to ongoing patent protection of Remicade. Due to differing patent legislation between EEA countries, Remsima and Inflectra were subsequently able to launch in Poland, Norway, Finland, Hungary and some other smaller Eastern European countries in approximately January 2014, whilst the originator patent protection remained in force in all other EU markets until February 2015. Therefore, there was significantly greater experience of biosimilar infliximab use in these four countries than in any other EU country, and these four countries constituted the initial list for a potential exchange visit.

As of June 2015, uptake, and therefore clinical experience, of biosimilar infliximab in Hungary and Finland was relatively poor compared with Norway and Poland. The final decision to use Norway was made on the following basis:

- Norway operated an exclusive single national tender system for biologic medicines. This tender to market biosimilar infliximab (Remsima) was won in 2014 and 2015 by Orion Pharmaceuticals Limited, which marketed Remsima on behalf of Celltrion in Scandinavian countries. All biosimilar infliximab used in Norway was specifically Remsima. This was in contrast to Poland where much of the biosimilar infliximab used was Inflectra (marketed by Alvogen in Poland on behalf of Hospira)
- The Norwegian Medicines Agency had conducted a government sponsored 500 patient, randomised, double-blind trial to assess the safety and efficacy of switching from originator infliximab to Remsima (called NOR-SWITCH study). This ongoing study had received publicity in the UK and Napp believed the delegates would value the opportunity to meet with some of the study investigators and discuss their experiences with Remsima as part of this trial
- The Norwegian healthcare system was similar in structure to the NHS, ie exclusively publicly funded in contrast to the Polish healthcare system which was a public-private hybrid system. Napp believed that more valuable discussions and insights would be obtained from meeting international colleagues

working in a similarly organised healthcare system hence the reason for selecting Norway as the location to share best practice.

Napp submitted that as a similar biosimilar, Remsima was granted a marketing authorization on the basis of a relatively new and little understood regulatory pathway. Biosimilars were biological medicinal products that were developed as copies of already existing biological medicines ie they could be conceptualised as being 'generics' of biological medicines. However, due to the high complexity and heterogeneity of biological medicines it was not possible to develop a chemically identical copy of a biological medicine, as could be done for a traditional 'small molecule' chemical medicine. Biosimilars could not therefore be authorised via a generic regulatory pathway which clinicians were familiar with, yet authorisation of these products required extensive physicochemical and *in vitro* characterisation rather than the extensive clinical trial data package that was a prerequisite for the grant of marketing authorization for a new medicine. Consequently, a 'hybrid' licensing pathway was developed for biosimilar products, whereby limited clinical data was required for the grant of a marketing authorization for all of the same therapeutic indications as the originator biological medicine by extrapolation.

With regard to Remsima, the regulatory authorities advised Celltrion that pivotal clinical trials of the product were undertaken only in the rheumatology conditions of rheumatoid arthritis (RA) and ankylosing spondylitis (AS), as the clinical endpoints as clinical markers of improvement were well defined and validated.

In the UK most infliximab was administered intravenously in hospital as a day case in inflammatory bowel diseases such as Crohn's disease (CD) and ulcerative colitis (UC). Rheumatologists in the UK mainly used subcutaneously administered biological therapies to treat RA and AS for greater patient convenience as this did not require hospital attendance. As outlined above no controlled clinical trials were required or conducted in CD and UC. Remsima was thus launched in the UK in a completely unprecedented position; as a 'new' biological medicine that lacked any clinical data in the most common gastroenterology indications of CD and UC. Dissemination of real-world evidence and peer-to-peer sharing of real-world experience of use of Remsima in CD and UC was critical in providing gastroenterologists with the knowledge and confidence to use it for these conditions. The necessity of sharing this real-world experience was made very clear to Napp in pre-launch advisory boards for Remsima. Napp provided the excerpts from a gastroenterologist and specialist gastroenterology nurse advisory board to illustrate the point.

PANEL RULING

The Panel noted that the agenda for the meeting at issue, which was sent to delegates, stated that the focus of the event was to share best practice in the treatment of IBD in both the UK and Norway, to facilitate discussion about the standard of care in Norway compared with the UK and to identify areas

of best practice in both countries. It was further stated that discussions would also focus on the introduction of biosimilars for the treatment of IBD including clinician and patient experience in Norway. The front cover of the agenda stated 'This meeting is organised by Napp Pharmaceuticals. Discussion of Napp Pharmaceuticals' products will take place at this event'. Prescribing information for Remsima was on the back outside cover.

The meeting proposal certified by Napp stated that the meeting had been developed in response to feedback from pre-launch advisory boards that real world evidence and experience from clinicians who had used Remsima was important. Remsima had been available in Norway since January 2014 but was not launched in the UK until February 2015. Biosimilar infliximab in Norway had a 63% market share. One of the stated aims of the meeting was to allow key opinion leaders to share real world experience with Norwegian clinicians who used Remsima in IBD given that clinical data in IBD patients and practical experience in the UK of using biosimilar infliximab was very limited. The Panel noted Napp's submission that the meeting was promotional; the agenda showed that two presentations on the first morning were specifically about initiating or switching treatment with Remsima. The Panel further noted Napp's submission that the Norwegian Medicines Agency had conducted a government sponsored 500 patient, randomised, double-blind trial to assess the safety and efficacy of switching from originator infliximab to Remsima (the NOR-SWITCH study). As the study had received some publicity in the UK, Napp believed the delegates would value the opportunity to meet with some of the study investigators and discuss their experiences with Remsima as part of this trial. Notwithstanding tours of two university hospital gastroenterology clinics included on the agenda, in the Panel's view the meeting was organised specifically with a focus on Remsima and to promote switching from Remicade to Remsima in IBD.

In the Panel's view, the sales force briefing about the meeting, which listed the criteria for inviting potential delegates, further emphasised the importance of Remsima to the meeting for Napp as opposed to sharing best practice as stated on the agenda. The potential delegates appeared to have been chosen for their ability to influence decisions about the use of Remsima. Delegates had to fulfil the following criteria:

'Secondary care healthcare professionals with an interest in gastroenterology medicine from each region who fulfil the following criteria:

- Will benefit from the educational agenda at the Norway IBD Exchange
- Are recognised as a national or regional opinion leader
- Will be involved in early education or decision making in relation to the use of Remsima and would benefit from understanding about the real world usage of Remsima in Norway

And who also fulfils one of the following additional criteria;

- Have training and education responsibilities at a national or regional level

- Have presented at local, regional or national meetings and congresses
- Have a history of producing key publications in gastroenterology
- Have a history of commissioning in gastroenterology.'

With regard to follow-up of the March delegates, the Panel noted Napp's submission that two had provided services to Napp since the exchange meeting; one had attended an advisory board regarding biosimilar infliximab uptake in London in July 2015 and the other authored a Remsima promotional advertorial which was published in a journal and attended an advisory board regarding biosimilar infliximab uptake in London in July 2015. With regard to the October delegates, Napp had provisional plans to ask two of them to speak at future promotional meetings but nothing was confirmed to date. The Panel noted that Napp's submission on this point appeared contrary to its statement that there had been no particular follow up with any of the delegates of the March or October meetings by Napp head office staff and Napp promotional staff had not been asked to follow up with attendees. In that regard the Panel also noted Napp's submission that of the 21 delegates at the October meeting, only 1, a specialist nurse had begun switching and 2 were considering switching.

The Panel noted that the supplementary information to Clause 22 stated that meetings organised by pharmaceutical companies which involved UK health professionals at venues outside the UK were not necessarily unacceptable. There had, however, to be valid and cogent reasons for holding meetings at such venues. These were that most of the invitees were from outside the UK and, given their countries of origin, it made greater logistical sense to hold the meeting outside the UK or, given the location of the relevant resource or expertise that was the object or subject matter of the meeting, it made greater logistical sense to hold the meeting outside the UK. As with meetings held in the UK, in determining whether such a meeting was acceptable or not, consideration must also be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, subsistence provided and the like. As with any meeting it should be the programme that attracted delegates and not the associated hospitality or venue.

The Panel noted that the meeting in question was the second of its kind. The first Norway IBD Exchange had been held in March 2015. The October 2015 meeting proposal form submitted by Napp indicated that due to the excellent feedback from March it had been decided to repeat the event. That feedback from a meeting was positive did not mean, by that very fact, that it was appropriate to take UK health professionals outside the UK or that the meeting otherwise complied with the Code. The Panel noted that the feedback form from the March meeting asked the delegates (questions 9 and 10) to rate the two hospital tours; everyone thought they were, good, very good or excellent. Similar feedback was obtained from the October meeting. Question 11 was 'After what you have heard discussed at the meeting, has this helped reassure you about using biosimilars in your own clinical practice?'; everyone from the March meeting answered 'Yes'

and some specifically referred to switching. Similar responses were given by those attending the October meeting. All but one of the delegates indicated that they thought the March meeting would have an impact on how they managed their IBD patients (question 12). Two delegates from the October meeting did not think the event would change how they managed patients. Again, some of the respondents from both meetings referred to switching.

Turning to the meeting at issue (the October Norway IBD Exchange) the Panel noted that it was wholly for UK health professionals; the delegates comprised 10 specialist nurses, 10 consultant gastroenterologists and one IBD Fellow. Three hospitals each had two delegates at the meeting. In addition six Napp staff attended. The speaker panel consisted of two UK clinicians and two Norwegian professors.

The Panel noted Napp's submission that the meeting allowed key opinion leaders to share real world experience with Norwegian clinicians who used Remsima in IBD given that clinical data in IBD patients and practical experience in the UK of using biosimilar infliximab was very limited. The Panel considered that this submission was at odds with Napp's explanation about the comparability of biosimilars and that 'Remsima was infliximab just as much as the many batches of originator Remicade were infliximab'. The Panel further noted Napp's submission that the EMA had stated that Remsima was highly similar to the originator and had not shown any clinically meaningful differences as part of its submission.

The Panel noted that the meeting agenda included tours of the gastroenterology clinics of two local university hospitals. Napp submitted that such tours were so that delegates could see how the biosimilar infliximab was delivered in a real-life clinical setting and speak to clinicians and specialist nurses at the hospitals who had actually administered the product. The Panel noted from the leavepiece at issue in Point B below however, that in terms of switching from Remicade to Remsima, it was claimed, *inter alia*, that 'Your clinic won't need to change how it does things' and that there was 'no need for new staff training'. In the Panel's view, although the UK delegates would have a professional interest in seeing the Norwegian clinics, such tours were not integral to the main focus of the meeting. In the agenda given to delegates both tours of the hospitals appeared to be identical in that both would include an overview of the clinic, standards of care and best practice with anti-TNF therapy, patient flow through the system, consultations, infusion procedure, capacity planning and the efficient running of clinics. In the briefing given to the chair and co-chair of the meeting, each of whom would host one of the hospital tours, less detail was given in that it was stated that during the tours it would be 'good if some of the clinic nurses are available, to hear their perspective and views on such things as the infusion procedure, capacity planning, and information that is given to patients to support them'. Overall the Panel considered that it would have made much more logistical sense to have the two Norwegian clinicians, and the IBD nurse specialist from Oslo, visit the UK to discuss their experiences and relevant patient case histories with their UK counterparts. Alternatively, the Panel queried

whether the meeting could have been conducted on-line. It appeared that the two hospital tours had been included to help justify the meeting being held in Norway. Given the lack of a clear and cogent reason to hold the meeting outside the UK, the Panel ruled a breach of Clause 22.1.

The Panel noted that the delegates had been invited to a two day meeting in Norway, the primary objective of which appeared to be to allay their concerns about switching IBD patients from Remicade to Remsima. The average total cost of hospitality, to include air fares, was £799.73 per person. The Panel considered that in and of itself, the hospitality had not been excessive although two evening meals each of just over £61 per head was on the limits of acceptability bearing in mind the relevant requirements of the Norwegian Code. Nonetheless, the Panel considered that hosting UK delegates for a two day promotional meeting in Norway, in circumstances where the Panel did not consider that there was a clear and cogent reason for holding the meeting outside the UK, was an inducement to prescribe or recommend Remsima. A breach of Clause 18.1 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that the supplementary information to Clause 2 stated that, *inter alia*, one activity likely to be in breach of Clause 2 was an inducement to prescribe. The Panel noted its comments above and its ruling of a breach of Clause 18.1 and thus considered that holding the meeting in question in Norway was such as to bring discredit upon and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

During its consideration of this matter the Panel was concerned to note that the presentation on initiating and switching treatment with Remsima appeared to refer to a dose of Remsima which was not in accordance with the particulars listed in the SPC. Slide 10 referred to a dose of 300mg Remsima in a patient who weighed 50kg. An asterisk beside the patient's weight took the reader to a statement which read 'The licensed posology for Remsima in moderate to severe [Crohn's disease] is 5mg/kg'. The Panel noted that the supplementary information to Clause 7.2 stated that claims must be capable of standing alone; in general, claims should not be qualified by the use of footnotes and the like. The Panel queried the acceptability under the Code of referring to a 6mg/kg dose of Remsima and requested that Napp be advised of its concern in this regard.

APPEAL BY NAPP

Promotional nature of the meeting

Napp noted that the Panel had highlighted that the meeting was promotional in nature and concluded that 'Notwithstanding tours of two university gastroenterology clinics included on the agenda, in the Panel's view the meeting was organised specifically with a focus on Remsima and to promote switching from Remicade to Remsima in IBD'.

Whilst Napp agreed that the meeting was promotional it strongly disagreed with the Panel's conclusion that the trip was specifically focused only on Remsima and switching from Remicade to Remsima. There was a much larger content of non-Remsima related education exchanging the clinical management, service delivery and healthcare organisation of IBD in Norway and UK.

The timings were as follows:

- 9.25 hours total meeting agenda (excluding breaks and travel time)
- 1.5 hours (~16%) on two presentations on the clinical use of Remsima in both new and switch patients by Norwegian expert gastroenterology professors
- 7.75 hours (~84%) spent on IBD clinical management and practical visits to the two hospitals.

Furthermore, Napp submitted that the two hospital tours, which were carefully planned and an integral component of the visit rather than an afterthought as suggested by the Panel, comprised 3.5 hours (38%) of the meeting. If it had not been possible to tour the two national IBD centre hospitals in Oslo then the meeting would not have been held.

Napp agreed that this was a promotional meeting but with a highly predominant (~84%) educational and practical discussion on all aspects of the management of IBD patients, contrasting the practices in UK and Norway.

Napp submitted that it made it clear in its response above that the agenda was conceived as having clear educational content (as per Clause 22.1 supplementary information) and organised by the medical department. However because Remsima would be discussed, as well as other biosimilar and originator products, Napp viewed it as a promotional meeting and so all related materials were certified as promotional, and included all obligatory information in accordance with Clause 4.2.

Selection of delegates

The Panel stated that criteria for delegate selection '... further emphasised the importance of Remsima to the meeting for Napp as opposed to sharing best practice as stated on the agenda.' and 'The potential delegates appeared to have been chosen for their ability to influence decisions about the use of Remsima'.

Napp agreed that one of the selection criteria for health professionals was their ability to influence decisions about the use of Remsima. Of equal importance was that they were recognised as a national or regional opinion leader and would benefit from the educational agenda, which included sharing best practice. Four further selection criteria were also applied, with delegates having at least one of the following:

- Training and education responsibilities nationally or regionally
- Presented at local, regional or national meetings and congresses

- A history of producing key publications in gastroenterology
- A history of commissioning in gastroenterology.

Napp submitted that these criteria ensured that the delegates were appropriate health professionals to educate their peers and implement service improvements after the IBD exchange meeting. The speaker faculty included two recognised UK gastroenterology key opinion leaders who presented UK IBD best practice, whilst two eminent Norwegian professors of gastroenterology, presented Norwegian IBD practice. There were no promotional presentations given by Napp staff. Napp therefore disagreed with the Panel's conclusion that the meeting was predominantly about promoting Remsima.

Napp understood that the Code did not prohibit companies selecting health professionals to be promoted to, based on their ability to influence decisions about the use of specific products. This was indeed the daily activity of the pharmaceutical industry promoting to health professionals.

Subsequent delegate 'follow-up' and consultancy

Napp noted that the Panel ruling discussed the fact that two of the March meeting delegates had subsequently provided consultancy services to Napp, and that Napp had provisional plans to approach two further delegates to provide consultancy services. The Panel ruling then noted that '... Napp's submission on this point appeared contrary to its statement that there had been no particular follow up with any of the delegates ...'.

Napp submitted that there had been no particular follow up with any of the delegates. Napp made this submission in response to the first of three questions (see below) as part of the Panel's request for further information:

- '4. What follow up has there been with attendees of the Norway IBD exchange meetings? Have any of the delegates been contracted to present or provide any other services on behalf of Napp Pharmaceuticals following their attendance at one of the Norway IBD exchange meetings? Was there any follow up on or monitoring of Remsima use following these exchange meetings?'

Napp submitted that this request for further information consisted of three distinct questions, which it interpreted as mutually exclusive and not directly connected when answering them. Napp's response to the first question was that there had been no particular 'follow up' which it interpreted to mean specific 'visit' to delegates post Norway trip. Napp's response to the second question stated that two of the March delegates had subsequently acted as consultants, and that Napp was considering similarly approaching two of the October delegates. These activities would have occurred irrespective of whether the health professionals involved had attended Norway or not, since they were consultant gastroenterologists with relevant sub-specialty expert knowledge of IBD. Napp apologised if its response appeared contradictory on this point, and hoped its reasoning was now clear.

The Panel also noted that the meeting in October was the second to be held in Norway and commented 'That feedback from a meeting was positive did not mean, by that very fact, that it was appropriate to take UK health professionals outside of the UK ...'. The second meeting in October was not held simply due to positive feedback from the March delegates. Commercial (IMS market share) data in July 2015, when it was decided to conduct another Norway trip, highlighted that Remsima usage was very low (1% of UK infliximab market) and feedback from clinicians was that there was still an educational need to understand biosimilars. Napp took the feedback from the March meeting into account insofar that 100% of the delegates confirmed the meeting had helped to reassure them about using biosimilars in their own clinical practice. With all of this information Napp considered that repeating the Norway meeting was appropriate. Finally, when the meeting was arranged there were no UK hospitals with significant experience of treating patients with biosimilar infliximab, and therefore no associated clinical service changes.

Acceptability of meetings outside the UK

The Panel detailed the criteria by which it might be considered acceptable for a pharmaceutical company to organise a meeting outside of the UK. The Panel quoted directly from the supplementary information to Clause 22.1 'There had, however, to be valid and cogent reasons for holding meetings at such venues [outside the UK]. These were that ... given the location of the relevant resource or expertise that was the object or subject matter of the meeting, it made greater logistical sense to hold the meeting outside the UK'.

Napp reiterated that it carefully considered this meeting in relation to the supplementary information to Clause 22.1; in its view, given the location of the relevant resource and expertise, there were valid and cogent reasons for conducting this meeting in Norway.

Legitimacy of the educational need regarding biosimilars (I)

Napp noted that the Panel had noted its submission that the meeting allowed key opinion leaders to share real world experience of use of Remsima in IBD, given that clinical data in IBD patients and practical experience of using the product in the UK was very limited. The Panel further noted that Remsima and Remicade were highly similar medicines with no clinically meaningful differences between the two. Napp submitted that the ruling then stated that the Panel considered these two submissions to be 'at odds', ie it implied that learning about practical use of Remsima could not be an adequate justification for the meeting when the practical use of Remsima was apparently identical to that of Remicade.

Napp submitted that the introduction of the world's first monoclonal antibody biosimilar (Remsima) to gastroenterologists who had had no previous experience with other biosimilars and also with no clinical data in IBD brought with it significant educational and practical considerations. Napp submitted that the Panel was correct that gaining both educational and practical experience of the use

of biosimilar infliximab (Remsima) in IBD was an objective of the meeting, but not the main one. The Panel was also correct to note that Remicade and Remsima were highly similar biological medicines. However the high similarity of Remicade to Remsima did not preclude the significant need to educate IBD specialists in the practical use of biosimilar infliximab (Remsima). This was further supported by a September, 2015 NHS England publication entitled 'What is a biosimilar medicine' along with several others cited in Napp's original response.

Napp referred to its response above in which it submitted that not only were Remsima and Remicade highly similar (as the Panel had noted), but also that this fact was commonly misunderstood or confused by health professionals, ('What is a Biosimilar', NHS England, Weise *et al*, 2012, Kurki 2015, Van der Plus *et al*, 2015, and Weise *et al*, 2014). Napp referred to statistics from a recent independent survey of European gastroenterologists conducted by the European Crohn's and Colitis Organization (ECCO), (Danese *et al*, 2015).

- The majority of respondents (70%) were aware that a biosimilar was a similar copy, but not equal to the originator, 19% responded that it was a copy of a biological agent, identical to the originator (like a generic), with a further 8% confusing a biosimilar with a different anti-TNF agent, like adalimumab to infliximab. **[ie 30% of gastroenterologists did not have a basic conceptual understanding of what a biosimilar was.]**
- The responders ranked as the main issue of biosimilars a different immunogenicity pattern than the originator (67%), while only 6% of respondents stated that there were no additional issues. **[Increased immunogenicity of a biosimilar product compared to its corresponding reference product would strictly preclude authorisation, therefore 67% of gastroenterologists were mistaken in this belief]**
- When asked if they would feel confident in prescribing biosimilars to their patients, most **(61%) felt little or no confidence in using biosimilars in their everyday clinical practice**, 26% felt confident enough to use biosimilars, 8% were very confident, and 5% were totally confident. **(Emphasis added)**

Napp submitted that the Panel ruling was incorrect with regard to a lack of need for education on biosimilars. Napp submitted that there was a legitimate educational need regarding biosimilar infliximab, and in Norway where there was the relevant resource and expertise not present in the UK when the meeting was organised. The educational legitimacy of the meeting was further substantiated by the results of the delegate feedback which Napp had previously communicated to the Panel. One delegate sent the following unsolicited feedback: 'I found the trip extremely educational – it will certainly change several aspects of my day-to-day practice!' – gastroenterology consultant.

The Panel stated that the leavepiece at issue in point B demonstrated, *inter alia*, that there was no educational need surrounding biosimilars, due to the inclusion of the claims 'Your clinic won't need to change how it does things' and 'no need for new staff training'.

Legitimacy of the educational need regarding biosimilars (II)

Napp submitted that the two abbreviated leavepiece quotations by the Panel were presented out of context. The full quotation made it clear that these statements referred specifically and only to the reconstitution, dilution and intravenous administration of Remsima. It did not follow that there was no educational requirement around biosimilars – it was simply designed to reassure clinicians that the preparation and intravenous administration of Remsima was the same as for Remicade.

Importance of the hospital tours, justification of the location and breach of Clause 22.1

The Panel further stated that '... although the UK delegates would have a professional interest in seeing the Norwegian clinics, such tours were not integral to the main focus of the meeting'. The reasons cited were that the agenda for the two hospital tours appeared to be identical and that the briefing given to the two meeting chairs (and hosts of the two hospital tours), was not sufficiently detailed/prescriptive in terms of the tour contents.

The Panel further stated that 'It appeared that the two hospital tours had been included to help justify the meeting being held in Norway', before concluding that it would have made more logistical sense to bring the two Norwegian clinicians and IBD nurse specialist to the UK, or that the meeting could have alternatively been conducted online. Therefore the Panel did not consider there had been a clear and cogent reason to hold the meeting outside the UK, and ruled no breach of Clause 22.1.

Napp submitted that the agendas for the two hospital tours were both similar, but not identical, because of differences between the hospital facilities, gastroenterology layout and service operations. However, as the hospital tours comprised 3.5 hours (38% of the entire agenda, Napp strongly disagreed that the hospital tours were 'not integral to the main focus of the meeting', nor 'had been included to help justify the meeting held in Norway'. As detailed above the majority of UK gastroenterologists and IBD specialist nurses had little or no confidence in the practical use of biosimilars.

Napp submitted that in planning the meeting two Napp medical staff twice visited the two Norwegian gastroenterology professors who co-chaired the meeting and hosted the hospital tours to discuss in detail the arrangements and logistics of the agenda and the hospital tours. The first meeting was held on 10 November 2014 where the Napp staff proposed a draft agenda. The hospital tours were always an integral part of the meeting since biosimilar infliximab was administered as an infusion in the hospital setting only. As outlined in the meeting proposal the hospital tours focused on:

- An overview of the gastroenterology clinic set up and facilities
- Standards of care and best practice with anti-TNF therapy in the management of IBD patients at these national centres of excellence in the

management of IBD

- How patients flow through the hospital system
- Patient outpatient facilities and consultations
- Infusion room set up, medicine handling and infusion procedures
- Capacity planning – how was this approached?
- Running clinics most effectively to improve efficiencies.

Napp submitted that it was particularly important that delegates saw how biosimilar infliximab infusions had been incorporated into the Norwegian IBD clinics, how the department managed the aseptic preparation of two brands of infliximab, how the medicine was administered and spoke to clinicians, nurses and patients about their experiences of biosimilar infliximab, providing food for thought and reassurance for the visiting UK health professionals.

Napp submitted that at the initial meeting the professors agreed the hospital tours were a vital element of the agenda and sought permission from their hospital managers that UK delegates could be shown around. Indeed one of the professors stated 'yes we could travel to UK to tell about our experience, having discussions, but showing our department, areas, locations, organisations, nurse led IBD visits - would never been the same'. Napp reiterated that without permission to conduct the tours, the meeting would not have gone ahead.

Napp submitted that on 2 March 2015 the two Napp medical staff visited Oslo to finalise the hospital tour agendas. They spent two hours at each of the hospitals touring each with the professors. They discussed what would be important for the delegates to see as well as who it would be important for the delegates to meet and speak with, including senior and junior gastroenterology clinicians, IBD specialist nurses and patients. Further to these verbal briefings, the speaker contracts for the two professors clearly stated 'when you give the UK clinicians a tour of the clinic', thus confirming the hospital tours were expected to occur.

Napp submitted that there were also several differences in the practicalities of the physical set up and organisation of the gastroenterology services within the UK and also between the two Norwegian hospitals, which were both national centres of excellence. Napp submitted that there was a legitimate educational need for delegates to gain first-hand clinical experience and understanding of the specialised resources and expertise within Norway. When the meeting was held in October there was no such equivalent hospital in UK which could match that found in Norway.

Napp submitted that with regard to visiting two hospitals in Norway, the analogy could be drawn of visiting one hospital in UK and concluding that all hospitals operated the same way without consideration to its surroundings and facilities. At the macro level they might be, but not at the more detailed level of service provision, physical surroundings/facilities, equipment, staffing, resources, capacity planning etc. In the case of the two hospitals they contrasted gastroenterology services at a hospital with old buildings physical surroundings and design, vs a sleek

modern state of the art highly automated and digital hospital. Indeed one of the IBD specialist nurses stated 'The 2 hospital visits were very interesting. The new state-of-the-art hospital vs the old fashioned one that I am used to'.

Napp refuted the Panel's claim that '... it would have made much more logistical sense to have the two Norwegian clinicians, and the IBD nurse specialist from Oslo visit the UK to discuss their experiences and relevant case histories with their UK counterparts.' '... or be conducted on-line'. If the meeting had only involved a series of educational presentations then Napp would agree. Clearly this would have not been a possibility for the hospital tours due to lack of resources in the UK and the expertise found in Norway. The hospital tours did not consist only of discussions with the two clinicians and IBD nurse specialist, as asserted by the Panel. On the contrary, the hospital tours included:

- Several opportunities for the delegates to meet and converse with a number of IBD clinical staff of varying roles and responsibilities regarding all aspects of their roles
- Direct observation and discussion of the infusion suite facilities, capacity issues, logistics of patient databases and experiences of any clinical issues when infusing originator or biosimilars
- Direct observation and discussion of the medicines dispensing, storage, reconstitution and preparation facilities used for infusions
- Direct observation and discussion of the quality and layout of the endoscopy suites and associated facilities in the two hospitals
- A visit to the outpatient consulting rooms to meet and discuss patient flow and how the IBD specialist nurses run their own patient consultations
- An opportunity for the delegates to meet and talk with IBD patients who had received or were in the process of receiving intravenous biological medicine infusions, including Remsima. This provided reassurance that the biosimilar was tolerated as an infusion just as for the originator medicine, Remicade
- Direct observation and contrasts of the logistics and distribution systems within the two hospitals
- A demonstration of how registry data was captured in an on-line electronic database, which then fed into the national IBD registry (something which the UK IBD community was trying to emulate)
- A meeting in his research laboratory with an eminent scientist at one hospital who discovered and developed one of the primary diagnostic tests used by IBD clinicians (faecal calprotectin). This also was an opportunity for him to discuss some of his more recent research activities
- A meeting with the wider nurse team about how they keep up-to-date and share knowledge with IBD nurse networks across Norway.

Photographs which showed the delegates during the tour of the two hospitals were provided.

Napp submitted that when the meeting was held, the objectives above could not have been met by visiting

a UK hospital because this experience did not exist (both in terms of the amount of biosimilar infliximab usage and long term follow up). Obviously, it would not be possible to transport all facilities, staff, and patients from Norway to the UK for this purpose. Napp submitted that the Panel's suggestion that the meeting could have been conducted online was an unsatisfactory proposal. If this were the case then videoconferencing would have replaced national and international conferences and other multi-participant meetings, which had not happened. The limitations and difficulties of conducting multi-participant teleconferences were well known. In this particular case what could not easily be reproduced was the 360 degree view of each area of the hospital when accompanied by fellow health professionals. This facilitated discussions and observations of room layouts eg of the endoscopy suite and of the infusion suite, where the infusions were prepared. Also even basic observations contrasting the ultra-modern facilities of one hospital with the older hospital. Additional feedback was sought from delegates as a result of this complaint, and Napp provided comments from various delegates to support the importance of the hospital tours. (Napp similarly noted that the PMCPA Guidance on Appeal Procedures Point 7 (Hearing by the Appeal Board), stated that joining an appeal meeting by teleconference was not viable.

In conclusion, the two contrasting hospital tours were highly educational and a practical unique resource in accordance with Clause 22. It would not have been logistically possible to conduct the hospital tours in the UK nor online. Napp therefore strongly disagreed that there was not a 'clear and cogent reason' for conducting the meeting in Norway, and therefore appealed the Panel's ruling of Clause 22.1.

Cost of hospitality

The Panel noted that the cost of '... hospitality had not been excessive although two evening meals each of just over £61 per head was on the limits of acceptability bearing in mind the relevant requirements of the Norwegian Code'.

Napp noted that the figure of '£61 per head' was from its response which preceded the actual visit to Norway when maximal predicted costs were certified. These were then monitored to ensure they did not exceed this limit. As stated previously the cost for dinner on the first night was £44.97 per head, and £54.06 per head on the second night. Napp would respectfully contest the Panel's use of the phrase '... on the limits of acceptability ...' in this context. Napp submitted that the use of this phrase seeks to characterise Napp's conduct as unacceptable. The Norwegian Code of Practice asserted a strict quantitative limit (£63) to the cost of a dinner which was clearly not exceeded, therefore no unacceptable conduct had occurred.

Inducement to prescribe and breach of Clauses 18.1, 9.1 and 2

Napp noted that the Panel ruled that as there was no clear and cogent reason for holding the meeting outside the UK, the meeting constituted a breach of Clause 18.1, and consequently a breach of Clause 2.

Napp submitted that it had carefully explained that there were clear and cogent reasons for the meeting to take place in Norway. The meeting was not intended to be an inducement to prescribe, nor was it perceived as such by the delegates or faculty. All hospitality was within established cost guidelines, air travel was economy class, travel within Norway was by group coach or economy class train, the hotel used was not luxurious, there was no scheduled time in the agenda for social or tourist activities other than one dinner outside the hotel, and there was a very busy educational schedule. In fact one delegate commented on how 'jam-packed' the educational agenda was and that he had 'worked extremely hard' during the meeting.

Napp submitted that the meeting was designed and intended to meet a legitimate educational need amongst gastroenterology specialists and IBD specialist nurses regarding the practical experience of implementing biosimilar infliximab into clinical practice. When the meeting was held this could only have been realistically achieved by taking delegates to Norwegian IBD centres of excellence which had already significant clinical experience of Remsima for over a year. Napp therefore appealed the Panel's ruling of Clauses 18.1, 9.1 and 2.

Concluding remarks

Contrary to the complainant's allegations, Napp submitted that it had always upheld the highest standards with respect to the Code, and had provided detailed explanations for its actions. Napp was shocked and upset to receive the anonymous complaint about the Norway meeting. The meeting was not an inducement to prescribe or a reward for switching and certainly not a 'junket'. Napp continued to defend the care and attention in planning and conduct of this highly educational, promotional meeting. Napp considered that the sharing of real-world experience provided important practical evidence of the safety and effectiveness of biosimilars in clinical practice. It also provided a better understanding for clinicians to allay their concerns and those of their patients and give them the confidence to use biosimilars in appropriate patients. Napp submitted that this was a rational and responsible course of action.

APPEAL BOARD RULING

The Appeal Board noted Napp's submission that Remsima was the world's first monoclonal antibody biosimilar of infliximab. Napp further submitted that the process by which biosimilars were granted a marketing authorization posed a unique challenge to clinician understanding, and health professionals were confused and lacked confidence about biosimilars. Napp submitted that there was a significant and legitimate educational need relating to the clinical use of biosimilar infliximab in the UK. The evidence required for Remsima's licence was to show that it and the reference medicine (Remicade) were essentially the same biological substance and clinical studies were only confirmatory. The Appeal Board noted Napp's submission that in the case of infliximab the clinical studies were not in gastroenterology

but that extrapolation from rheumatology studies to IBD was possible based on the overall evidence of comparability. Thus there was less direct data on the clinical efficacy and safety of Remsima in gastroenterology than would have been available for Remicade. When Remsima was launched in the UK (February 2015), clinical data in IBD and practical clinical experience with biosimilar infliximab was extremely limited. The Appeal Board further noted Napp's submission that Norwegian clinics, however, had used Remsima since early 2014; the position by June 2015 was that Remsima was used for all new IBD patients nationally and several IBD centres had switched to 100% Remsima.

The Appeal Board noted that apart from the originator medicine, Remicade, which had been on the UK market for 15 years, there were now two biosimilar infliximabs available, Remsima and Inflectra. The Appeal Board noted Napp's submission that planning for the October meeting had started in June at which time only one or two centres in the UK were using Remsima. In that regard, however, the Appeal Board noted that a National Institute for Health and Care Excellence (NICE) report, 'Introducing biosimilar versions of infliximab: Inflectra and Remsima', published 31 July 2015 and provided by Napp, stated that between April and June 2015 one UK hospital had switched 150 IBD patients from Remicade to the biosimilar infliximab, Inflectra. The Appeal Board thus noted that shortly after starting to plan the meeting in question, there was published data which referred to relevant experience of switching gastroenterology patients to biosimilar infliximab in the UK, albeit short-term data compared with the longer term use of a biosimilar infliximab in Norway.

The Appeal Board noted that delegates to the meeting had toured the two Norwegian hospitals in groups. The tours of the two hospitals lasted in total 3.5 hours. In the newer hospital the group size was ten with smaller groups touring the older hospital. In that regard the Appeal Board queried whether the group sizes and the relatively short time spent in each hospital were compatible with the delegates being able to observe and absorb meaningful, relevant details about service provision, patient flow, logistics etc.

The Appeal Board noted that the supplementary information to Clause 22 stated that meetings organised by pharmaceutical companies which involved UK health professionals at venues outside the UK were not necessarily unacceptable. There had, however, to be valid and cogent reasons for holding meetings at such venues. In the Appeal Board's view, given the evidence required for Remsima's marketing authorization that there was no difference in the use, dose or preparation of Remicade and Remsima, and there was UK experience of switching IBD patients from Remicade to a biosimilar infliximab, there was no clear and cogent reason for the UK delegates to travel to Norway for the meeting. That was not to say that some way could not have been found of incorporating the Norwegian experience into a meeting held in the UK. Nonetheless, the Appeal Board upheld the Panel's ruling of a breach of Clause 22.1. The appeal on that point was unsuccessful.

The Appeal Board noted that UK delegates had attended a two day meeting in Norway, which had

been paid for by Napp. The Appeal Board considered that although the level of subsistence had not been excessive, hosting UK delegates for a two day Remsima promotional meeting in Norway, where there was no clear and cogent reason for holding that meeting outside the UK, was an inducement to prescribe or recommend Remsima. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 18.1. The appeal on that point was unsuccessful.

The Appeal Board noted its rulings above and considered that high standards had not been maintained and it upheld the Panel's ruling of a breach of Clause 9.1. The appeal on that point was unsuccessful.

The Appeal Board noted that biosimilars were emerging therapies which due to the way in which they were granted a marketing authorization meant that, as with Remsima, direct clinical data might not be available in all therapy areas. Health professionals in therapy areas where the direct clinical data might be lacking needed to understand and have confidence in that process. In that regard the Appeal Board considered that whilst the location of the meeting was not unreasonable, the aim of the meeting was not unreasonable. The Appeal Board noted its rulings and comments above and decided that on the facts of this case, a ruling of a breach of Clause 2 would be disproportionate. On balance, the Appeal Board ruled no breach of Clause 2. The appeal on that point was successful.

B Remsima Leavepiece (ref UK/REMS-15078)

The leavepiece was entitled 'Your guide to changing treatment Remicade → Remsima'.

COMPLAINT

The complainant provided a copy of a leavepiece which explained the process for switching treatments. The complainant was very concerned that the UK pharmaceutical industry continued to pursue such an aggressive stance on switching between treatments with little concern for patients, or patient safety. There was no reference in the leavepiece to the conditions which either of the medicines in question were used to treat, and it was even suggested that there should be no safety concerns associated with switching to Remsima, despite being a recently licensed medicine with limited safety information. The complainant submitted that this type of irresponsible action by the pharmaceutical industry put patient's safety, and indeed lives, at risk.

The complainant summarised his/her complaint by stating that this type of activity did nothing for the reputation of either Napp or the UK pharmaceutical industry as a whole. More worrying was the effect that this negligent and unethical behaviour would have on patients. [This comment was taken by the Panel to apply equally apply to the meeting at issue in Point A above and the leavepiece].

When notified of the complaint, Napp was asked to respond in relation to Clauses 2, 7.2, 7.9, 7.10 and 9.1 of the Code.

RESPONSE

Napp disagreed that switching from an originator biologic to a biosimilar version of infliximab was pursuing an 'aggressive stance on switching between treatments with little care for patients, or patient safety'. The leavepiece in question which promoted a switch was created as a supplementary item in response to health professionals' requests for clarity around how to switch, ie as a practical guide to changing treatment (a copy of the switch leavepiece briefing, (ref UK/ REM-15078a) was provided). For example, several health professionals were confused over whether they could use the biosimilar infliximab in patients who had previously had an adverse reaction to the originator infliximab. This was addressed on pages 2 and 3 of the leavepiece when emphasising eligibility criteria. Furthermore, page 3 of the leavepiece highlighted in a grey box that 'the decision to switch should still always be done on a case-by-case basis with the consent of the treating physician and the patient'. Napp submitted that the leavepiece promoted the rational use of Remsima and in that regard the company had not promoted aggressive switching and had carefully considered patient safety.

Napp noted that the front page of the leavepiece stated that 'Prescribing information can be found on the back' which listed all the licensed indications for Remsima. Thus the complainant was incorrect to assert that there was no mention of the conditions which either of the medicines in question were used to treat.

Napp further noted that point 2 on page 4 of the leavepiece also stated clearly and with references that 'The dosing and posology of Remsima is identical to Remicade across all licensed indications'. Furthermore, the leavepiece was left only with secondary care specialist health professionals who were also very familiar with infliximab; Remicade had been licensed in the UK for over 15 years (EMA approval, 13 August 1999).

The complainant stated that the leavepiece even suggested that there should be no safety concerns associated with switching to Remsima, despite it being 'a recently licensed medicine with limited safety information'. Napp assumed that this specifically related to page 6 of the leavepiece headed 'What to Expect after Switching'. The totality of current evidence (as per Clauses 7.2, 7.9 and 7.10) demonstrated the lack of any meaningful difference in clinical safety, efficacy or immunogenicity of biosimilar and originator infliximab. This included extensive regulatory *in vitro*, and controlled clinical trial data and was supplemented with post-marketing *in vitro* and *ex vivo* immunogenicity data, as well as increasing amounts of real-world clinical outcomes data.

Furthermore, the complainant did not explain why switching from an originator to a biosimilar was irresponsible and could 'put patient's safety, and indeed lives at risk'. As discussed above, Napp assumed that the complainant fundamentally misunderstood the concept of biosimilarity.

The overarching regulatory guidance explicitly stated that, 'The ultimate goal of the biosimilar comparability

exercise is to exclude *any relevant differences* between the biosimilar and the reference medicinal product' (emphasis added). The EMA position had been further clarified in a publication co-authored by a number of senior employees of the EMA, the Medicines and Healthcare products Regulatory Agency (MHRA) and other European regulatory agencies, which stated, 'Undoubtedly, biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products'.

Patient populations had also on many occasions been exposed to changes in the molecular characteristics of their biological medicines that were directly comparable to the differences seen between originator and biosimilar medicines. It was therefore incorrect to suggest that Remsima was an 'irresponsible action by the pharmaceutical industry [which] puts patients safety and indeed lives at risk' implying that there was 'no clinical experience' in these types of changes.

Napp noted the wider European perspective on the switching to biosimilar infliximab from the originator product. Several European medicines regulatory agencies advocated switching to biosimilar infliximab – some (eg Denmark) actively mandated a switch for economic as well as clinical considerations. In some countries large-scale switches had therefore already occurred, resulting in uptake of ~70%, ~90% and ~38% for biosimilar infliximab in Norway, Denmark and Finland respectively. It was therefore misinformed and not credible to suggest that up to 90% of infliximab patients in some European countries had been treated irresponsibly.

Napp further noted the recent document from the NICE, 'Introducing biosimilar versions of infliximab: Inflectra and Remsima', the recent set of documents published by the PrescQIPP organisation about implementation of biosimilar infliximab, and the letter routinely sent from a UK hospital when patients were switched. All three of these authoritative UK organisations addressed the issue of switching from originator to biosimilar medicines and concluded that it was rational and responsible.

Counter to the complainant's proposition that switching a patient was an 'irresponsible action by the pharmaceutical industry [which] puts patient's safety, and indeed lives, at risk', section 4.4 of the NHS England document 'What is a Biosimilar Medicine?' answered the question of switching a patient to a biosimilars as follows:

'4.4 Can a patient already established on an originator biological medicine be switched to a biosimilar medicine?

There is growing practical NHS experience that demonstrates the safety and efficacy of biosimilars in clinical practice. The evidence regarding interchangeability is still developing. Guidance across some EU Member States currently recommends that switching between a reference product and its biosimilar (and indeed amongst biosimilar medicines) should be managed at the discretion of the individual prescriber in partnership with the patient, with appropriate monitoring in place. Evolving evidence and

treatment guidance should be made available to patients and prescribers to support them in their decision-making.’

In conclusion Napp submitted that the leavepiece complied with Clauses 7.2, 7.9 and 7.10. Napp had not stated that Remsima had no adverse reactions and safety had been qualified to encourage rational use without exaggeration or misleading claims. Napp had maintained high standards by careful consideration of how to promote switching without jeopardising patient safety. Napp submitted that it had not brought discredit upon, or reduced confidence in the pharmaceutical industry. Napp denied breaches of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that the leavepiece at issue was a guide to changing treatment from Remicade to Remsima. In that regard the Panel noted that it was not unacceptable under the Code for a company to promote a simple switch from one product to another; companies could not, however, assist a health professional in implementing a switch. The leavepiece explained that Remsima was infliximab and a biosimilar of Remicade. It was stated that patients currently on Remicade could therefore be changed to Remsima treatment providing they were eligible. In that regard the Panel did not consider that it necessarily had to be stated in the main body of the leavepiece which conditions patients would be treated for; in any event, the Remsima prescribing information on the back of the leavepiece listed the licensed indications for the medicine. The Panel noted that the leavepiece listed those patients who would not be eligible for Remsima treatment

(eg those who had previously had to discontinue Remicade therapy due to intolerance or lack of efficacy) and those who would be eligible (ie those who currently responded well to or remained stable on Remicade). In addition it was stated that any switch should always be done on a case-by-case basis. Having listed which patients might or might not be eligible for a switch, the leavepiece described how the switch should be carried out and what to expect after switching. On the back of the leavepiece was a highlighted box of text with additional safety information about the risk of tuberculosis during and after treatment with [Remsima].

The Panel did not consider that the leavepiece suggested that there were no safety concerns with Remsima as alleged. No breach of Clause 7.9 was ruled. The Panel considered that on the basis of the information before it, there was nothing to show that the leavepiece had not encouraged the rational use of the medicine; the eligibility or otherwise of patients had been made clear. No breach of Clause 7.10 was ruled. The Panel did not consider that the information in the leavepiece was misleading. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above and did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

Given its rulings above, the Panel also ruled no breach of Clause 2.

Complaint received **18 September 2015**

Case completed **14 March 2016**

SANOFI GENZYME v AMICUS

Promotion of a medicine to a patient organisation

Genzyme (now Sanofi Genzyme) complained about a 30 minute presentation given by Amicus Therapeutics at a meeting of a patient organisation international network held in the UK in November 2015. Genzyme was concerned about references to Amicus's product migalastat which did not have a marketing authorization.

Genzyme explained that Amicus had claimed that its presentation was for the purpose of disease awareness and which was made to an audience of patient association representatives, patients and health professionals.

Genzyme recalled that most of the presentation was a review of the clinical development of migalastat including the phase I, II and III study designs, continuation protocols detailing the indications, investigational uses and dosing regimens. Genzyme alleged that this was 'product awareness', not disease awareness, which promoted migalastat before the grant of its marketing authorization.

Genzyme further alleged that promotion of a medicine and particularly an unlicensed one at a patient organisation meeting was in breach of the Code.

Genzyme submitted that lack of a reference number on the presentation raised concerns over a robust review and approval process from appropriately qualified and registered personnel in accordance with the Code. During inter-company dialogue, Amicus stated that all of its material was thoroughly reviewed and the presentation had been reviewed and approved by appropriate medical, legal and regulatory practitioners along with a large international law firm. Genzyme alleged that the process described did not comply with the Code.

Genzyme alleged that the breaches were gross and broad in scope, constituted a failure to maintain high standards and undermined the standing of the pharmaceutical industry in breach of Clause 2.

The detailed response from Amicus is given below.

With regard to Genzyme's concern that the presentation at issue promoted migalastat before the grant of a marketing authorization. The Panel noted five slides (21-25) referred to migalastat studies, including phase III studies, and provided details of study designs including dosage and/or endpoints. No clinical results from the studies were given. Slide 26 was headed 'Next Steps for Migalastat' and stated that the European Medicines Agency's (EMA) review of the marketing authorization application for migalastat remained on track under accelerated assessment and that the Committee for Medicinal Products for Human Use

(CHMP) opinion was anticipated by early 2016. In the Panel's view, this slide at the very least implied that the results from the clinical trials were positive. In that regard the Panel considered that claims had been made for migalastat contrary to Amicus's submission that it had provided no information about the product.

The Panel considered that it was immaterial that the presentation did not refer to any specific clinical results; merely raising awareness of studies would draw attention to, and encourage interest in them. This was especially so given that the audience primarily comprised leaders of national patients' organisations. In the Panel's view, reference to the encouraging regulatory status of migalastat would prepare the delegates for a new product entry in 2016. Although the legitimate exchange of medical and scientific information was permitted during the development of a medicine, the presentation at issue was, in the Panel's view, the straightforward provision of information; there was apparently no information exchange between the presenter and the delegates. In that regard the presentation could not take the benefit of the exemption to the Code. Overall, the Panel considered that the presentation had promoted migalastat prior to the grant of its marketing authorization and a breach of the Code was ruled.

The Panel noted the alleged breach of the Code in that the meeting at issue had included patients and patient representatives. The Code prohibited the promotion of prescription only medicines to the public. The Panel noted that although not everyone at the meeting was a health professional, those that were not were senior executives of the international network organisation or of relevant national patient organisations. The Panel noted from the meeting programme that the primary aim of the international network was to facilitate collaboration between patient organisations around the world to support those affected by Fabry Disease. The Panel considered that, in the context of a patient organisation expert meeting, the executives that had been invited to attend were not members of the general public *per se*. In that regard, notwithstanding its ruling of a breach of the Code above, the Panel ruled no breaches of the Code.

The Panel noted that Amicus acknowledged that the presentation aimed at an audience of patient organisations although reviewed by senior company employees, had not been formally certified and breaches of the Code were ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure. In that regard the Panel noted that migalastat had been promoted prior to the grant of its marketing authorization; the patient organisation international network had been given information such as to expect a possible new product entry in 2016. Further, the presentation at issue had not been formally certified before use. On balance, a breach of Clause 2 was ruled.

Upon appeal by Amicus the Appeal Board considered that the pharmaceutical industry should be able to inform patient groups about medicines and/or general research interests. Companies, however, had to ensure that the provision of such information complied with the Code including the differences between proactive provision and reactive provision. The audience at the patient organisation expert meeting were all senior officials of various patient groups worldwide. The Appeal Board noted that the Panel had considered that, in the context of the meeting in question, the patient organisation executives were not members of the public *per se*. The Appeal Board noted, however, that this matter was not before it for consideration and thus made no comment on this decision. In the Appeal Board's view attendees at the meeting were likely to take messages back to their respective organisations.

The Appeal Board noted that slides 21-25 of the presentation gave an overview of clinical trial protocols for migalastat studies. Slide 23 referred to monotherapy for patients with amenable mutations. The Appeal Board noted that mutation analysis and the possibility of targeting therapy to patients with particular gene mutations was an emerging concept in the treatment of Fabry Disease. It noted Sanofi Genzyme's submission that patient suitability characteristics for migalastat such as amenable and non-amenable mutations were discussed. The Appeal Board noted that the slides presented at the meeting referred to the need for patients to know their mutation as this could impact on symptoms and their treatment. According to the presentation the registration studies were carried out on patients with amenable mutations. Amicus's representatives at the appeal confirmed that amenable mutations were mentioned at the meeting including which ones might be relevant to migalastat. The representatives at the appeal stated that it was a matter for the regulators to decide which would be included in the marketing authorisation/SPC. Slide 26 was headed 'Next Steps for Migalastat' and gave an overview of the regulatory status of the medicine. It was stated that the EMA review of the marketing authorization application for migalastat remained on track under accelerated assessment and that the CHMP opinion was anticipated by early 2016. In the Appeal Board's view, these statements together implied a positive outcome.

The Appeal Board noted the statements and discussion about amenable mutations and the implied positive regulatory status of migalastat. Although much of the information was in the public domain, on balance, the Appeal Board considered that the presentation had raised the prospect of a new treatment for Fabry patients with amenable

mutations and in that regard, had promoted migalastat prior to the grant of a marketing authorization. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its ruling above and considered that as the promotional presentation was not formally certified it upheld the Panel's ruling of a breach of the Code. The appeal on that point was unsuccessful. The Appeal Board considered that as the presentation was aimed at a patient organisation and had not been formally certified it upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and rulings above and considered that high standards had not been maintained and consequently upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

Although noting its comments above, the Appeal Board did not consider that in the particular circumstances of this case a ruling of a breach of Clause 2 was warranted and so the Appeal Board ruled no breach of that clause. The appeal on this point was successful.

Genzyme (now Sanofi Genzyme) complained about a presentation given by Amicus Therapeutics at a meeting of the patient organisation international network, held in the UK in November 2015. Genzyme was concerned about references to migalastat which did not have a marketing authorization.

COMPLAINT

Genzyme explained that Amicus had claimed that its 30-minute presentation was for the purpose of disease awareness. Amicus would not give Genzyme a copy of its presentation and so Genzyme stated that its complaint was based on its recollection of the meeting itself, but without documentation. The presentation was made to an audience of patient association representatives, patients, and health professionals.

Genzyme stated that over 20 minutes of the presentation was devoted to a comprehensive review of the clinical development activities for migalastat. The presentation included details of the phase I, II and III study designs including continuation protocols with details of the indications, investigational uses and dosing regimens. Genzyme alleged that this was 'product awareness', not disease awareness, and thus promoted migalastat prior to the grant of its marketing authorization in breach of Clause 3.1.

Genzyme further alleged a breach of Clause 26.1 given that the meeting included patients and patient representatives and the presentation was promotional.

Genzyme noted that Clause 27.2 described '... the prohibition on advertising prescription only medicines to the public (Clause 26.1)' in the context of working with patient organisations. Genzyme

alleged that promotion of an unlicensed medicine at a patient organisation meeting was in breach of Clause 27.2.

Genzyme submitted that the presentation did not appear to have a UK reference number which raised concerns over a robust review and approval process from appropriately qualified and registered personnel in accordance with the Code. This point had been raised previously in inter-company dialogue in order to encourage Amicus to develop proper processes. On this occasion Amicus stated in inter-company dialogue: 'Additionally, as we have described to your company in the past, all Amicus material is thoroughly reviewed in accordance with a clear process by a review board known internally as the 'Copy Review Board' and the presentation made at [the patient organisation meeting] is no exception having been reviewed and approved by appropriate medical, legal and regulatory practitioners along with a large international law firm'. Genzyme did not consider that the process so described complied with the Code and alleged breaches of Clauses 14.1, and 14.3.

Genzyme considered that the breaches were gross and broad in scope and had been wilfully and serially perpetrated despite its numerous attempts at constructive inter-company dialogue. This constituted a failure to maintain high standards in breach of Clause 9.1.

In their entirety and in view of the repeated breaches in the face of failed inter-company dialogue, Genzyme alleged that Amicus had undermined the standing of the pharmaceutical industry in the eyes of both patient associations and health professionals in breach of Clause 2.

RESPONSE

Amicus submitted that contrary to Genzyme's assertion that it had claimed that the presentation at issue was for the purposes of disease awareness, Amicus was well aware that its slides did not consist *exclusively* of disease awareness. In inter-company dialogue, Amicus characterised the presentation as including *both* disease awareness *and* corporate communications. Almost all of the slides presented consisted of corporate information and disease awareness information. For example, 16 of 27 slides consisted of title and sub-heading slides, an agenda slide, a corporate mission slide, a corporate development pipeline slide, a headquarters and offices slide, slides regarding the company's patient advocacy department and its corporate mission, a cost of drug development slide, and a slide on publicly known regulatory timelines. Additionally, 6 of 27 were legitimate disease awareness slides presenting facts about the disease.

Amicus stated that Genzyme's complaint was arguably about slides 21-25 which provided a high-level general overview of the company's AT-1001 study design and endpoints. While these slides might not fit squarely within the categories of disease awareness or corporate information, they were not promotional. Genzyme had tried to characterise the information in these slides as

'product awareness' so as to provide the necessary bridge to promotion. But product awareness implied knowledge about the benefits and risks of a product. If an individual had no knowledge about the benefits or risks of a product, no knowledge about that product's efficacy or safety profile, then he/she could not have any awareness about it. Amicus stated that since it provided no information about the characteristics, features, benefits or risks of its investigational product, it could not have engaged in product awareness. Indeed, in the 5 slides at issue, and in the rest of the presentation, no results were disclosed regarding product efficacy or safety and no other product characterisations were made which might encourage, or be perceived to encourage, the use of product.

Amicus submitted that the 5 slides provided high-level 'study awareness'. Like disease awareness, study awareness was not promotional. It was not designed to convince or to encourage an audience to take specific action, but was rather intended to raise general awareness regarding the existence of a study without disclosing any results. As the first Amicus UK employees were hired in 2015 and the first UK office formally opened in November 2015, the purpose of the presentation was to raise awareness of Amicus itself (corporate slides) and to explain at a high level what it was working on (study awareness slides). The audience at this patient organisation expert meeting consisted of its board of directors and the leaders of country patient organisations that were members (28), healthcare specialists (7), and representatives from industry (8). This was not a general patient meeting or patient support event, and Amicus did not present to an audience of general patients. The patient organisation leadership, like the leadership of other patient advocacy organisations, was very sophisticated regarding the disease affecting its members and its minimum expectation of the pharmaceutical industry was that it kept it aware of the existence, name, and profile of companies investigating treatments for the disease affecting its membership and that the industry kept it aware at a high level of relevant investigations.

Amicus stated that in its view, the sharing of this minimal information was a basic responsibility to the leadership of these patient advocacy communities. The company understood that it could not disclose any actual results, and it did not do so. No data was disclosed, nor any statements made, about product efficacy, benefits, safety or any other data. Nor did Amicus encourage use of an investigational product. Amicus believed this understanding was consistent with EU law and the directive against promotion of a prescription-only medicine to patients because the intent was basic awareness, not product promotion. Amicus noted that the European Court of Justice had made clear that the key basis for distinguishing non-promotional information from advertising was the purpose of the communication. In this regard, Amicus submitted that the slides spoke for themselves. Not only were they devoid of product data and characterisation, but they also had no branding (no brand name, brand designs or logos, no marketing messages). Nor were there any product comparisons or superiority claims. None of

the hallmarks indicative of promotion were present in the slides.

Amicus hoped that based on the information above, and after review of the information below, the Panel would agree that the presentation at the patient organisation's expert meeting was not advertising because its purpose was to provide non-promotional corporate, disease awareness, and limited study awareness information without seeking to promote the prescription, supply, sale, or consumption of a medicine.

With regard to Clause 3.1, Amicus noted that Genzyme had alleged that over 20 minutes was devoted to a comprehensive review of the clinical development activities for migalastat. As set out above, this was incorrect. Most of the presentation (22 of 27 slides) consisted of corporate information and disease awareness information. Genzyme then proceeded to allege that the 5 slides which provided a high-level general overview of the AT-1001 study design and endpoints constituted promotion. As described at length above, simply providing a high-level overview of a study's parameters to a sophisticated audience of patient organization leaders and healthcare specialists for the purpose of providing 'study awareness', without providing any results or encouraging use, could not constitute promotion because the intent was not to induce the prescription, consumption, administration, purchase, sale, supply or use of a product.

Moreover, pursuant to the transparency requirements in the laws and codes of many jurisdictions, these basic study parameters had to be publicly disclosed in a manner accessible to patients, healthcare providers and others and in that regard Amicus referred to Clause 9 of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Code of Practice which stated that 'it is recognized that there are important public health benefits associated with making clinical trial information more publicly available to healthcare practitioners, patients and others' and that companies 'disclose clinical trial information' as set forth in the codes of many jurisdictions. The purpose of these transparency and public health requirements was 'study awareness' so patients, health professionals and others could have basic awareness of ongoing trials. Indeed, these laws and codes implicitly recognized the important distinction between 'study awareness' (which was required) and 'product awareness'. In Amicus's case, the basic study parameters shared at the meeting were already publicly available and accessible on the clinicaltrials.gov website pursuant to the company's transparency obligations; Amicus stated that it did not go beyond study awareness by disclosing efficacy and safety data that would transform its presentation into product awareness.

With regard to Clause 26.1, Amicus noted that Genzyme alleged that the presentation advertised a prescription only medicine to the public. Such an allegation was a gross mischaracterisation of the presentation and of the limited audience. First, the patient organisation expert meeting was not a general patient meeting or patient support event.

Amicus stated that it did not present to an audience of general patients. Rather, the patient organisation expert meeting was a small invitation-only meeting. The audience consisted of approximately 28 leaders of patient organisations, 7 healthcare specialists and 8 industry representatives. The supplementary information to Clause 26.2 provided examples of situations in which information could be deemed to have been disseminated to the public, including dissemination of information to journalists through press conferences, press announcements, television or radio reports, public relations activities, posters in spaces available to the public and information posted on websites. The common theme in all these examples was that information became accessible to the public. The presentation at issue was made to a small number of invited individuals at a closed-door meeting and was not otherwise made publicly available. Secondly, as set out above, the presentation was not in substance or intention promotional. Since the presentation was neither promotional advertising nor disseminated to the public, it could not constitute advertising to the public. A breach of Clause 26.1 was denied.

Amicus noted that Clause 14 required certain written materials to be reviewed and approved internally before they could be used with external audiences. Clause 14.1 applied to promotional materials and Clause 14.3 applied to non-promotional materials. Amicus submitted that as the presentation was non-promotional, Clause 14.1 was not applicable.

The presentation at issue was reviewed internally a week before the meeting. Unfortunately, one of the company's UK signatories had gone on sick leave about two weeks earlier. Amicus engaged an alternative signatory from 8 December 2015. Thus, Amicus acknowledged that between 3 November and 8 December 2015 it was a signatory short. A senior manager stepped in as reviewer during this time. Amicus stated that it released no materials without them first being reviewed and approved by a competent medical reviewer to ensure their medical and scientific accuracy. In addition to the review by the manager, the slides presented at the patient organisation expert meeting were also reviewed and approved by senior company officials from the legal and regulatory departments pursuant to the company's process as well as by a large international law firm and by an additional authorised signatory. All of these reviewers agreed that the slides were factual, objective, non-misleading and non-promotional under the Code and EU law for the reasons described above. The reviewers approved the presentation for a single use consistent with the venue, date and audience specified on the introductory slide.

Amicus submitted that although it did not have a UK approval certificate for the presentation given a signatory's sick leave, it thoroughly reviewed the substance of the presentation to ensure that it complied with the Code in all other respects. Additionally, as described above, although the company was short of one signatory during November, this role was carried out by a contractor until the return of the permanent employee from

sick leave. Amicus stated that it now had a detailed UK standard operating procedure to ensure that all UK materials were reviewed and approved before being used externally to ensure compliance with the Code (a copy was provided). Amicus hoped that it had been able to convey that it was fully aware of its responsibilities under the Code, that it took those responsibilities very seriously and that it had made every effort to comply with the Code to date despite the unexpected sick leave of a UK signatory, its very limited UK resources and the very recent opening of its UK office in November 2015.

Amicus noted Genzyme's allegation that 'the breaches were gross and broad in scope and had been wilfully and serially perpetrated'. In that regard, Amicus noted that Genzyme had misleadingly invoked clauses that did not apply in the context of an investigational product without a label that was not on the market, a small closed-door meeting of patient organisation leaders and healthcare specialists and slides that consisted of corporate and disease awareness information and 5 high-level study awareness slides.

Genzyme had also misleadingly mischaracterised the nature and content of the slides. For example, Genzyme alleged that most of the presentation was devoted to a comprehensive review of clinical development activities. This was not so. There were only 5, high-level study awareness slides which did not disclose any actual data.

Thirdly, Genzyme had also tried to make it seem as though there had been repeated breaches associated with several materials when the only material at issue in this case was the presentation. For example, Genzyme alleged that breaches had been 'serially perpetrated' and even that 'in view of repeated breaches' Clause 2 had also been breached. Given that no materials had previously been found in breach of any code or law in any jurisdiction, Amicus submitted that Genzyme's language was intentionally calculated to create the impression of a pattern of inappropriate behaviour.

Amicus stated that the essence of this case was whether 5 slides which provided a high-level general overview of the AT-1001 study design and endpoints, presented to a small audience of patient organisation leaders and healthcare specialists without any general patients in the audience, and without disclosing any actual efficacy or other data, constituted pre-approval promotion. For all of the reasons provided above, Amicus stated that the slides were not promotional. The company aimed to raise general awareness about the organisation (corporate slides) and to explain at a high level what it was working on by sharing limited, publicly available information from clinicaltrials.gov (study awareness slides).

Amicus submitted that the Panel had ruled in other cases that if materials did not fit squarely within one of the exemptions to the definition of promotion, those materials would still be deemed non-promotional when the totality of the facts and circumstances made clear on balance that the

material was not promotional. For example, in Case AUTH/2651/11/13, although the information displayed at a scientific conference did not 'satisfy the requirements for the legitimate exchange of medical and scientific information during the development of a medicine', the Panel nevertheless concluded that the information presented did not amount to the promotion of an unlicensed medicine and no breach of Clause 3.1 was ruled. Although the context of the current case was different from Case AUTH/2651/11/13 in that the presentation was to a limited audience of patient advocacy leaders at a patient advocacy leadership meeting, and not to health professionals at a scientific conference, the cases were very similar in that multiple facts in each case pointed to the non-promotional substance and intent of the presentations at issue and on balance both were non-promotional.

Amicus reiterated that its slides were devoid not only of product data and characterisations, but also of product comparisons, superiority claims and any elements of branding (no brand name, designs or logos, no marketing messages), thus the slides were neither promotional in substance nor in appearance. Additionally, the person who presented the slides was from Amicus's patient advocacy function not from sales or marketing nor was the presenter subject to any form of bonus incentive plan based on sales or product use. In fact, because the product was investigational as it had not been approved by any regulatory agency, Amicus had not developed or implemented a bonus incentive plan for any of its employees anywhere in the world. It was very clear to the audience at the meeting that the presenter was from patient advocacy and not from sales and marketing and that there was no actual promotion.

Amicus stated that contrary to Genzyme's portrayal of it, it was not a careless company. In fact, Amicus had made every effort to comply with the Code to date despite the unexpected sick leave of its UK signatory, its very limited UK resources and the very recent opening of its UK office in November 2015. The company took its responsibilities under the Code very seriously and understood the special nature of medicines and was committed to maintaining high standards at all times. Nothing in the presentation at issue could have caused offence or reduced the high standards expected of the pharmaceutical industry, so there was no breach of Clause 9.1. But most importantly, the presentation of high-level slides at the patient organisation expert meeting did not bring discredit to, or reduce confidence in, the pharmaceutical industry. The Panel had consistently held that a breach of Clause 2 was reserved to indicate particular censure; Amicus stated that considering all of the facts and circumstances in this case, a finding of a breach of Clause 2, on balance, was not warranted.

PANEL RULING

The Panel noted Genzyme's concern that the presentation at issue promoted migalastat before the grant of a marketing authorization. The company drew particular attention to a comprehensive review of the clinical development activities for migalastat.

Five slides (21-25) referred to migalastat studies, including phase III studies, and provided details of study designs including dosage and/or endpoints. No clinical results from the studies were given. Slide 26 (to which Amicus had not referred) was headed 'Next Steps for Migalastat' and stated that the European Medicines Agency's (EMA) review of the marketing authorization application (MAA) for migalastat remained on track under accelerated assessment and that the Committee for Medicinal Products for Human Use (CHMP) opinion was anticipated by early 2016. In the Panel's view, this slide at the very least implied that the results from the clinical trials were positive. In that regard the Panel considered that claims had been made for migalastat contrary to Amicus's submission that it had provided no information about the product.

The Panel considered that it was immaterial that the presentation did not refer to any specific clinical results; merely raising awareness of studies would draw attention to, and encourage interest in them. This was especially so given that the audience primarily comprised leaders of national patients' organisations. In the Panel's view, reference to the encouraging regulatory status of migalastat would prepare the delegates for a new product entry in 2016. Although the Panel noted that the legitimate exchange of medical and scientific information was permitted during the development of a medicine, the presentation at issue was, in the Panel's view, the straightforward provision of information; there was apparently no information exchange between the presenter and the delegates. In that regard the presentation could not take the benefit of the exemption to Clause 3.1. Overall, the Panel considered that the presentation had promoted migalastat prior to the grant of its marketing authorization and a breach of Clause 3.1 was ruled.

The Panel noted the alleged breach of Clause 26.1 in that the meeting at issue had included patients and patient representatives. Clause 26.1 prohibited the promotion of prescription only medicines to the public. The Panel noted that although not everyone at the meeting was a health professional, those that were not were senior executives of the patient organisation or of relevant national patient organisations. The Panel noted from the meeting programme provided that the primary aim of the international network was to facilitate collaboration between patient organisations around the world to support those affected by Fabry Disease. The Panel considered that, in the context of a patient organisation expert meeting, the patient organisation executives that had been invited to attend were not members of the general public *per se*. In that regard, notwithstanding its ruling of a breach of Clause 3.1 above, the Panel ruled no breach of Clause 26.1 and thus no breach of Clause 27.2.

The Panel noted that Amicus had acknowledged that the presentation, although reviewed by senior company employees from medical, legal and regulatory, had not been formally certified. A breach of Clause 14.1 was ruled. The Panel noted that Genzyme had also alleged a breach of Clause 14.3 which required certain materials, other than promotional materials but including,

inter alia, material related to working with patient organisations, to be certified. The Panel considered that as the presentation was aimed at a patient organisation, it required certification under Clause 14.3. As noted above, the presentation had been reviewed but not formally certified. A breach of Clause 14.3 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was seen as a sign of particular censure. In that regard the Panel noted that migalastat had been promoted prior to the grant of its marketing authorization; the patient organisation international network had been given information such as to expect a possible new product entry in 2016. Further, the presentation at issue had not been formally certified before use. On balance, a breach of Clause 2 was ruled.

APPEAL BY AMICUS

Amicus appealed all of the Panel's ruling of breaches of the Code.

Clause 3.1

Amicus submitted that this was a very important case because no pharmaceutical association in any country had ever addressed whether simply sharing the design and endpoints of a study during an international, closed-door meeting of patient organisation leaders, could be seen as pre-approval promotion. This had important implications for the pharmaceutical industry and for the leaders of patient organisations.

The appeal against this ruling was based in five key areas:

- 1 A factual update regarding regulatory status was non-promotional

This appeal related to 6 slides out of 27 (slides 21-26) which provided a high-level overview of study design and endpoints, as well as a factual update regarding the regulatory status of migalastat. Regarding slide 26, the regulatory update, Amicus submitted that it appeared the Panel might have misinterpreted the statement 'remains on track under accelerated assessment' to mean there was positive news about the application and/or that it was likely to be approved because the Panel stated that 'reference to the encouraging regulatory status of migalastat would prepare the delegates for a new product entry in 2016'.

The European update (slide 26) stated:

- European Medicines Agency's (EMA) review of the marketing authorization application (MAA) for migalastat remains on track under accelerated assessment
- Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated by early 2016.'

Amicus submitted that these were factual statements which were neither encouraging nor implied a positive outcome to the regulatory submission. 'Remains on track' demonstrated that Amicus was currently working with the EMA as part of the review process. 'Accelerated assessment' was a regulatory term well known to an audience of experts in rare and orphan disease, which simply described the type of process selected by the EMA to appraise migalastat. This was first announced by the EMA in a press release on 22 May 2015 (copy provided) which was publicly available via the EMA's website. Neither statement meant that there was positive or encouraging news about an application. The end result for an application reviewed under accelerated assessment might be positive or negative, just like any other regulatory pathway.

Amicus submitted that it was reasonable to conclude that if it had inferred an encouraging regulatory status it might imply a positive clinical outcome from the studies. However, Amicus had simply reiterated the regulatory process it was being assessed under and when it was anticipated to conclude. These facts, already in the public domain, did not imply anything and as such were non-promotional.

2 Sharing study design and endpoints was non-promotional

Amicus submitted that the key question was whether five slides, which provided a high-level general overview of study design and endpoints, when presented to a small audience of invited, international, patient organisation leaders, and without disclosing any actual efficacy or other data, constituted pre-approval promotion. For all of the reasons stated above, the presentation of this limited and high-level information was not promotional.

Amicus submitted that an important consideration in deciding if a communication was promotional was if it encouraged administration, consumption, prescription, purchase, recommendation, sale, supply or use of a medicine. The presentation did not use any language that encouraged use of a product; it was silent about the characteristics, features, benefits and claims relating to any product, and there were no elements of branding that were typically seen in promotional communications (no brand name, no brand designs or logos, no marketing messages). The fact that there was no promotional language or content in the slides provided strong evidence that the presentation was non-promotional.

Amicus submitted that it was tempting to quote the multiple regulations regarding clinical trial transparency (European Clinical Trial Regulation EMA/36398/2015: 'The information that will be made public for all clinical trials will include amongst other: the major characteristics of the trial; treatment population characteristics and number of subjects; inclusion and exclusion criteria, main objectives and endpoints'. Clause 9 of the International Federation of Pharmaceutical Manufacturers & Associations Code; European Federation of Pharmaceutical Industries and Associations/Pharmaceutical Research

and Manufacturers of America – Joint Principles for Responsible Clinical Trial Data Sharing to Benefit Patients (2014); ABPI – Clinical Trial Disclosure Toolkit; Section 801 of the US Food and Drug Administration Amendments Act) and to note that it was required by law and encouraged by the codes of many jurisdictions to transparently disclose study design and endpoint information. Amicus asked the Appeal Board to consider the intent of these regulations. The regulations were designed to ensure that patients had appropriate high-level understanding of the research undertaken by industry and by inference such study awareness was the responsibility of industry.

As further context, Amicus submitted that the PMCPA's Guidance about Clause 3 made clear that the role of the employee carrying out the activity had a contextual bearing on whether it was promotional. It was clear to the international audience that the Amicus executive who presented at the patient organisation expert meeting was a senior executive who sat on the company's corporate executive committee, with a global remit to ensure the company worked transparently and collaboratively with patient organisations across the world to benefit patients. The purpose of this presentation was to raise awareness of Amicus and to explain at a high level what the company was working on rather than promoting a product.

3 The reasoning in Case AUTH/2651/11/13 was applicable

Amicus submitted that whilst most non-promotional information provided during the pre-approval timeframe could be categorised as corporate information, disease awareness or scientific exchange, other information was not automatically promotional simply because it did not fit into one of those categories. As discussed above, to be promotional there must be language or evidence, such as features, benefits or claims, to demonstrate the promotional intent or purpose of the communication.

Amicus submitted that in Case AUTH/2651/11/13 the Panel recognised this important principle and ruled that the information disclosed in the posters did not 'satisfy the requirements for the legitimate exchange of medical and scientific information during the development of a medicine' and did not fit within any other exemption to the definition of promotion (eg was not corporate information or disease awareness information), the Panel nevertheless concluded that there had been no promotion. The posters did not amount to the promotion of an unlicensed medicine and no breach of Clause 3.1 was ruled.

Amicus urged the Appeal Board to recognize that the very limited category of information at issue in this case (study design and endpoints) was a clear example of information which, on its own, could not be considered promotional despite the fact that it did not fit within a pre-existing category of non-promotional information.

4 Public policy reasons for sharing study design and endpoints with patient organisation leaders

Amicus submitted that, not only was limited study design and endpoint information not promotional, there were strong public policy reasons why a pharmaceutical company should provide such information to patient organisation leaders who were key stakeholders in the healthcare system and yet often treated as being less entitled to basic healthcare information than other key stakeholders such as healthcare providers, regulators and even investors. By ruling against the presentation of limited, high-level information about study design and endpoints to patient organisation leaders while allowing (and even mandating) the disclosure of such information in other forums (for example, in the press, through public clinical trial registers, and to investors), the credibility and responsibility of patient organisation leaders to participate in appropriate engagement with the medicine development community became severely undermined. In contrast, having the right to basic study awareness allowed patient leaders to have a broad perspective on what companies were working on, which was essential to their mandate of developing initiatives, programmes, and awareness campaigns that were in the best interests of patients.

Amicus submitted that basic study design and endpoints were already publicly available via clinicaltrials.gov, press releases, physician conferences and also through industry media and published financial analysts' reports which were readily accessed through Google alerts and other means. Patient leaders often used such notifications to remain informed about key developments, and also used this information to raise issues and questions with industry. To state that patient organisation leaders must search through all of these sources to obtain basic study awareness information rather than obtain the same information directly from the pharmaceutical industry devalued the integral role played by patient leaders and harmed the industry's relationship with them.

Amicus submitted that, importantly, this case would set the tone for the industry's future relationship with patient organisation leaders. Companies could either recognise that patient organisation leaders were key stakeholders, entitled to basic awareness of studies and so foster a relationship of partnership between them and the industry or deny them even the most basic information about studies and industry or deny and limit the valuable role they could and should play in the system.

Amicus submitted that if the provision of even basic study design and endpoint information to patient organisation leaders was held to be promotional, even in the absence of any actual clinical data being presented, it would stop patient organisation leaders being able to receive such basic information from industry which was contrary to the intent of the transparency directives and could result in a loss of trust and respect for industry by one of its important stakeholders. This would fundamentally be at odds with the ABPI Guidance 'Working together, delivering for patients', which identified clarity of purpose, integrity, independence and transparency as the core tenants of working together.

5 This case could be used to provide an appropriate boundary for the pharmaceutical industry

Amicus submitted that although this was a precedent-setting case, the question at issue was very narrow, namely whether a presentation of the following should be ruled as pre-approval promotion:

- Simple design and endpoints of a study
- No sharing of any data collected in the studies
- A factual account of full, current regulatory status
- No features, benefits, or claims in regard of a product
- To a closed audience of international, expert, patient organisation leaders.

Amicus submitted that the great advantage of being able to narrowly frame the question was that a clear decision could be reached with identifiable boundaries and no confusion. If it was decided that providing such limited study design and endpoint information did not constitute pre-approval promotion, then the pharmaceutical industry would have a clear ruling that the provision of such information was permissible. The industry would also know that the provision of information that went beyond that of this case was not protected by the Appeal Board's ruling.

Clause 14.1

Amicus submitted that because Clause 14.1 applied exclusively to promotional materials, and because of the reason already submitted in its original response and appeal, Clause 14.1 did not apply and thus had not been breached.

Clause 14.3

Amicus submitted that in its response to the complaint it had attempted to show that it had followed appropriate processes and that all materials were carefully reviewed by qualified staff in the unfortunate absence of one of its signatories. Amicus appealed this clause to gain clarification. The content did not fall comfortably under any of the bulleted examples provided in Clause 14.3. Amicus referred to the supplementary information regarding other materials issued by companies which related to medicines but was not intended as promotional material for those medicines *per se* which required 'examination only'. Amicus accepted that if the Appeal Board decided that its presentation was defined by one of the bullets of Clause 14.3, then indeed it had breached that clause.

Clauses 9.1 and 2

Amicus reiterated, for reasons of context, that it hired its first UK employees in mid 2015 and formally opened its UK office in November 2015. As such, the purpose of the presentation was to raise awareness of the company with a corporate overview and to explain at a high level what it was working on regarding research and development. Indeed, Amicus submitted that it had acted with the highest ethical and medical standards (and always sought to

do so) and that its presentation was consistent with the Code and was in the best interests of patients.

Amicus submitted that its actions could not in totality be considered as not having maintained high standards, or indeed brought discredit on the industry. The intent of the presentation was company, disease, study and regulatory awareness. There were no reasons why this would be viewed as promotional. As such Amicus submitted that it was not in breach of Clauses 3.1, 14.1 and thus Clauses 9.1 and 2. With respect to Clause 14.3, Amicus asked for guidance regarding the applicability of these materials to this clause.

Consistent with the ABPI guide to collaboration between charities and pharmaceutical companies in the UK, 'Working together, delivering for patients', collaboration needed to be based on mutual understanding and Amicus submitted that a ruling of a breach of Clause 2 would send a conflicting message to patient organisations and was disproportionate.

COMMENTS FROM SANOFI GENZYME

Sanofi Genzyme noted Amicus submitted that its appeal related to 6 slides out of 27 – the complaint did not mention specific slides (these had never been made available to Sanofi Genzyme, despite a request to Amicus), but rather that Amicus's presentation and discussion about the clinical development of migalastat, comprised the majority of overall presentation. Sanofi Genzyme alleged that approximately 20 minutes of the total agenda was devoted to the presentation of the clinical development plan, and clinical aspects of migalastat use (such as patients with amenable or non-amenable genetic mutations). The number of actual slides was immaterial and did not reflect the likelihood of a breach of the Code having occurred.

Sanofi Genzyme noted that Amicus also stated that 'no pharmaceutical association in any country has ever addressed whether simply sharing the design and endpoint of a study, during an international, closed-door meeting of patient organisation leaders, can be seen as pre-approval promotion'. Sanofi Genzyme alleged that this was disingenuous as not only was a significant amount of time devoted to the clinical development programme for a medicine that had not received its marketing authorization, but there was also significant discussion of the meaning of amenable mutations, and from whom patients could seek advice on whether they had an amenable mutation. One of the physicians in the audience observed that Amicus was informing patients about the medicine and advising them to speak to their physician to see if they would be suitable for treatment, all in a pre-approval environment, and that Amicus should not be informing patients about the medicine, because it put the physician in an awkward position when patients asked whether they had an amenable mutation (as the physician in question had been asked by Amicus to sign a non-disclosure agreement on this subject). This highlighted that at least one of the non-industry physician members of the audience at this meeting was troubled by the pre-

approval activity of Amicus, driving potential patients to their physicians to enquire about an unlicensed product which the physician was unable to respond to due to being bound by confidentiality to Amicus.

Sanofi Genzyme noted that Amicus considered that the Panel might have misinterpreted the statement 'remains on track under accelerated assessment' to mean there was positive news about the application and/or that the application was likely to be approved. Amicus stated during the presentation 'At the moment, because we are in the process of regulatory approval, we've got to be careful', and 'when we market the [medicine], it will be on the SmPC' (emphasis added). So in addition to the content of the slides (and referred to by the Panel), this was reinforced by a spoken clear expectation for a positive outcome of the regulatory submission, and the subsequent marketing of the medicine was considered a certainty.

Sanofi Genzyme noted that Amicus also stated that the purpose of this presentation was to raise awareness of the company and to explain at a high level what the company was working on rather than promoting a product. Sanofi Genzyme alleged that as already stated, as approximately 20 minutes of a 30 minute presentation was devoted to discussing the entire clinical development plan for migalastat, the regulatory submission, and patient suitability characteristics such as amendable and non-amenable mutations (with respect to treatment), pre-approval promotion must be considered to be the primary focus of the presentation rather than general company awareness.

Sanofi Genzyme noted Amicus's submission that it could choose to either recognise that patient organisation leaders were key stakeholders, entitled to basic awareness of studies and so foster a relationship of partnership between them and the industry, or deny and limit the valuable role they could and should play in the system. Sanofi Genzyme alleged that this was a fallacious argument, and not what it had contended with its complaint. Sanofi Genzyme alleged that, on balance, the material presented by Amicus with the emphasis and focus (and majority of time) spent on presenting the clinical development programme and population of patients amenable for treatment in a specific indication of an unlicensed product amounted to pre-approval promotion, and that was what the focus of consideration should be. Sanofi Genzyme did not dispute the value of legitimate, appropriately timed and conducted engagement with patient organisations but it did not support the pre-approval promotion of uncertified material.

Sanofi Genzyme noted that Amicus had submitted that because Clause 14.1 applied exclusively to promotional materials, and because of the reasons submitted in its response and appeal, Clause 14.1 did not apply and this had not been breached. Sanofi Genzyme alleged that this was promotional material and promotional activity, given the nature and extent of the information presented and discussed relating to a product that had not received UK marketing authorization. Therefore Clause 14.1 had been

breached. Furthermore, in previous correspondence, Amicus had alleged that one of its signatories had gone on sick leave prior to this event, so therefore had no appropriately qualified medical signatory at the time of this event. Sanofi Genzyme was rather surprised, therefore, that having already supplied this explanation, in its appeal, Amicus now submitted that the reason for no medical signatory was because it believed one was not required. These two lines of argument were inconsistent, and raised questions over not only Amicus's understanding of the Code, but also its internal review, approval and certification processes.

Sanofi Genzyme asked the Appeal Board to uphold the Panel's rulings of breaches of Clauses 2, 3.1, 14.1, 14.3 and 9.1. Promotion of a product before it received its marketing authorization was a serious breach of the Code and was cited as an example of activity which was likely to be in breach of Clause 2.

* * * * *

It became apparent that Sanofi Genzyme had not received the copy of the letter providing the slides at issue. In response to being provided with a copy of the slides Sanofi Genzyme made the following additional response.

Sanofi Genzyme stated that the proportion of slides devoted to product in the presentation was very much less than the proportion of time devoted to discussion of product; Sanofi Genzyme made the latter point clearly in its previous submissions but could not compare it to the number of slides. Sanofi Genzyme also observed that the lengthy and detailed discussion, which it clearly recalled, on amenable mutations and recommendations by the company for patients to consult their doctor about these were not referenced in the slides.

APPEAL BOARD RULING

The Appeal Board considered that the pharmaceutical industry should be able to inform patient groups about medicines and/or general research interests. Companies, however, had to ensure that the provision of such information complied with the Code including the differences between proactive provision and reactive provision. The audience were all senior officials of various relevant patient organisation groups worldwide. The Appeal Board noted that the Panel had considered that, in the context of the meeting in question, the patient organisation executives were not members of the public *per se*. The Appeal Board noted, however, that this matter was not before it for consideration and thus made no comment on this decision. In the Appeal Board's view attendees at the meeting were likely to take messages back to their respective organisations.

The Appeal Board noted that slides 21-25 of Amicus's presentation at the meeting in question gave an overview of clinical trial protocols for migalastat studies. Slide 23 referred to monotherapy for Fabry patients with amenable mutations. The Appeal Board noted that mutation analysis and the possibility of

targeting therapy to patients with particular gene mutations was an emerging concept in the treatment of Fabry Disease. It noted Sanofi Genzyme's submission that patient suitability characteristics for migalastat such as amenable and non-amenable mutations were discussed. The Appeal Board noted that the slides presented at the meeting referred to the need for patients to know their mutation as this could impact on symptoms and their treatment. According to the presentation the registration studies were carried out on patients with amenable mutations. Amicus's representatives at the appeal confirmed that amenable mutations were mentioned at the meeting including which ones might be relevant to migalastat. The representatives at the appeal stated that it was a matter for the regulators to decide which would be included in the marketing authorisation/SPC. Slide 26 was headed 'Next Steps for Migalastat' and gave an overview of the regulatory status of the medicine. It was stated that the EMA review of the marketing authorization application for migalastat remained on track under accelerated assessment and that the Committee for Medicinal Products for Human Use (CHMP) opinion was anticipated by early 2016. In the Appeal Board's view, these statements together implied a positive outcome.

The Appeal Board noted the statements and discussion about amenable mutations and the implied positive regulatory status of migalastat. Although much of the information was in the public domain, on balance, the Appeal Board considered that the presentation had raised the prospect of a new treatment for Fabry patients with amenable mutations and in that regard, had promoted migalastat prior to the grant of a marketing authorization. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.1. The appeal on this point was unsuccessful.

The Appeal Board noted its ruling above and considered that as the promotional presentation was not formally certified it upheld the Panel's ruling of a breach of Clause 14.1. The appeal on that point was unsuccessful. The Appeal Board considered that as the presentation was aimed at a patient organisation and had not been formally certified it upheld the Panel's ruling of a breach of Clause 14.3. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and rulings above and considered that high standards had not been maintained and consequently upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

Although noting its comments above, the Appeal Board did not consider that in the particular circumstances of this case a ruling of a breach of Clause 2 was warranted and so the Appeal Board ruled no breach of that Clause. The appeal on this point was successful.

Complaint received **10 December 2015**

Case completed **11 April 2016**

ANONYMOUS, NON-CONTACTABLE v MYLAN

Exhibition stand design and hospitality

An anonymous, non-contactable complainant alleged that the majority of exhibition stands at a European congress held in London in 2015 were extremely extravagant and in poor taste considering today's economic climate. Three examples were given including that Mylan had an ice-cream stand. The complainant stated that there was a real party atmosphere rather than a true scientific congress atmosphere which he/she expected in such stands.

The detailed response from Mylan is given below.

The PMCPA's guidance on items at conferences and exhibition stands stated that the Code allowed the provision of hospitality at scientific meetings including from an exhibition stand; hospitality provided from an exhibition stand must be subsistence only and not such as to induce a delegate to visit the stand eg no more than non-alcoholic beverages, such as tea, coffee and water, and very limited quantities of sweets, biscuits or fruit. In the Authority's view hot dogs, ice-cream, waffles, etc should not be provided at exhibition stands.

The Panel noted Mylan's submission that frozen yoghurt rather than ice-cream was available from its stand. It was chosen to provide a healthy and balanced alternative to sweets or biscuits and the costs did not exceed the level which the recipients would normally adopt when paying for themselves. The Panel noted the cost per serving and the number of servings over the four day period.

The Panel considered that it was important for a company to be mindful of the impression created by its activities; perception and cost were important factors when deciding whether subsistence was appropriate. In the Panel's view, the availability of frozen yoghurt from the Mylan stand went beyond the provision of subsistence and was contrary to the requirements of the Code and a breach was ruled. High standards had not been maintained and a further breach was ruled.

The Panel noted that the complainant had made a general allegation that the majority of the stands at the congress were extravagant. The complainant, who had the burden of proving his/her complaint on the balance of probabilities, had not provided any material to support his/her allegations in this regard; it was not clear from the complaint what aspect of the stands were 'extremely extravagant and in poor taste considering today's economic climate'. As the complainant was non-contactable, it was not possible to obtain more information from him/her. A judgement had to be made on the available evidence. In the Panel's view the complainant had not shown that the Mylan exhibition stand was unacceptable as alleged. No breach of the Code was ruled.

An anonymous, non-contactable complainant who described him/herself as a UK health professional complained about exhibition stands at the European Society of Cardiology (ESC) Congress held in London 29 August – 2 September 2015.

COMPLAINT

The complainant stated that the majority of the stands at the congress were extremely extravagant and in poor taste considering today's economic climate. It showed that pharmaceutical companies had far too much money to splash around. Three examples were given including that Mylan had an ice-cream stand. According to the complainant, there was a real party atmosphere rather than a true scientific congress atmosphere which would be expected in such stands. The complainant provided photographic evidence of the Mylan stand and queried its acceptability.

When writing to Mylan the Authority asked it to respond in relation to Clauses 9.1, 9.7 and 22.1 of the 2015 Code.

RESPONSE

Mylan stated that the ESC was an international congress with over 30,000 registered delegates from all over the world and approximately 600 exhibitors.

Mylan was represented by the EPD global cardio metabolic team. The global EPD portfolio fell locally under BGP Products Limited which was currently a member of the ABPI. Mylan submitted that its stand design and all scientific items for distribution were reviewed and approved at both global and local level. The approval of the stand was also provided by the ESC. BGP Products Ltd could not comment on the atmosphere in the congress in general however it strongly disagreed that the Mylan stand had 'a real party atmosphere'.

Mylan noted that the complainant's statement that 'the majority of the stands at the congress were extremely extravagant' was a general comment that did not apply to the Mylan stand which was not 'extremely extravagant'.

Mylan provided a copy of the ESC floor plan which showed Mylan's stand location and size, which it submitted that considering the size of the ESC Congress and the surrounding stands, could be described as small to medium sized. The stand was designed to allow health professionals to engage in an appropriate scientific environment by providing seating to help facilitate scientific discussion between the Mylan international team and congress delegates. Product monographs, summaries of product characteristics (SPCs) and clinical paper

reprints were available on request. The stand was manned by the Mylan international team throughout the congress. The global and local teams ensured the stand environment and format was appropriate for an international congress of the size and magnitude of the ESC.

Mylan submitted that it provided tea and coffee from its stand. Frozen yoghurt, not ice-cream as alleged, was also supplied. The level of hospitality was approved by the global cardio-metabolic team.

The ESC instructed the global team that 'All catering offered within exhibit areas should be ordered from the official stand caterer'. The provision of frozen yoghurt was one of the services listed in the caterer's brochure. The Mylan stand did not have any signage advertising the availability of frozen yoghurt, nor was any frozen yoghurt handed out unsolicited. Congress attendees requested the frozen yoghurt as refreshment from one of the baristas provided by the official stand caterer. Mylan provided details of the cost of the hospitality provided on the stand over 4 full days of the ESC congress which included 4 staff to man the coffee and frozen yoghurt bar.

Mylan submitted that the hospitality provided from its stand, was intended to be subsistence only, no steps were made to induce a delegate to visit the stand. The provision of a frozen yoghurt bar was only taken to provide a healthy and balanced catering offer (vs sweets, or biscuits) for the delegates as per ESC's recommendations. Furthermore the hospitality costs did not exceed the level which the recipients would normally adopt when paying for themselves.

Taking the above into consideration BGP Products Ltd submitted it had not breached Clauses 9.1, 9.7 or 22.1.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure, anonymous complaints were accepted and like all complaints, judged on the evidence provided by the parties. Complainants had the burden of proving their complaint on the balance of probabilities. The Panel noted that it was not possible to ask the complainant for further information.

Clause 22.1 stated that hospitality must be strictly limited to the main purpose of the event and must be secondary to the purpose of the meeting ie subsistence only. The level of subsistence offered must be appropriate and not out of proportion to the occasion. Clause 22.1 applied to scientific meetings, promotional meetings, scientific congresses and other such meetings and training. The supplementary information to Clause 22.1 also stated that a useful criterion in determining whether the arrangements for any meeting were acceptable was to apply the question 'Would you and your company be willing to have these arrangements generally known?'. The impression that was created by the arrangements for any meeting must always be kept in mind.

The PMCPA's guidance on items at conferences and exhibition stands stated that the Code allowed the provision of hospitality at scientific meetings and the like and there was no reason why it should not be offered from an exhibition stand. Companies would have to be certain that the hospitality overall complied with the Code and that any hospitality provided from an exhibition stand was subsistence only and not at a level as to induce a delegate to visit the stand. In the Authority's view companies should provide no more than non-alcoholic beverages, such as tea, coffee and water, and very limited quantities of sweets, biscuits or fruit. The Authority advised that it did not consider that hot dogs, ice-cream, waffles, etc should be provided at exhibition stands.

The Panel noted Mylan's submission that frozen yoghurt rather than ice-cream as referred to in the complaint, was available from its stand. According to Mylan, it was one of the services listed in the caterer's brochure mandated by the exhibition organiser and was approved by Mylan's global cardio-metabolic team. It was chosen to provide a healthy and balanced catering alternative to sweets or biscuits for the delegates and the costs did not exceed the level which the recipients would normally adopt when paying for themselves. The Panel noted the cost *per serving* and the number of servings over the four day period.

The Panel considered that it was important for a company to be mindful of the impression created by its activities; perception and cost were important factors when deciding whether subsistence was appropriate. Services available from an exhibition caterer may not be appropriate for use by pharmaceutical companies. In the Panel's view, the availability of frozen yoghurt from the Mylan stand went beyond the provision of subsistence and was contrary to the requirements of Clause 22.1 of the Code. A breach of Clause 22.1 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that the complainant had made a general allegation that the majority of the stands at the congress were extravagant and showed that companies had far too much money to splash around. Clause 9.7 stated that extremes of format, size or cost of material must be avoided. The complainant, who had the burden of proving his/her complaint on the balance of probabilities, had not provided any material to support his/her allegations in this regard; it was not clear from the complaint what aspect of the stands were 'extremely extravagant and in poor taste considering today's economic climate'. As the complainant was non-contactable, it was not possible to obtain more information from him/her. A judgement had to be made on the available evidence. In the Panel's view the complainant had not shown that the exhibition stand was unacceptable as alleged. No breach of Clause 9.7 was ruled.

Complaint received **21 December 2015**

Case completed **2 March 2016**

ANONYMOUS, NON-CONTACTABLE v BOEHRINGER INGELHEIM

Symposia at a meeting

An anonymous, non-contactable complainant noted that medical symposia at a European congress held in London in 2015 included off-label discussions and discussions about grants for medical research while stating that prescribing information was available. The complainant thought that prescribing information was associated with promotion and provided a copy of a slide from a Boehringer Ingelheim symposium as an example. Boehringer Ingelheim marketed Pradaxa (dabigatran) which was a novel oral anticoagulant (NOAC).

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the slide was from a symposium entitled 'Your patients, your practice, your choice: NOACs in the clinic' which comprised four presentations focussing on the use of dabigatran. The complainant had not provided details of what he/she considered to be off-label. Conversely, Boehringer Ingelheim provided copies of all of the presentations and submitted that although two were about topics currently under debate with ongoing studies, both were in line with dabigatran's marketing authorization. Whilst Boehringer Ingelheim submitted that the fourth presentation referred to its reversal agent for dabigatran which did not have an EU licence the Panel noted it did not have a complaint in this regard and it was thus obliged to rule no breach of the Code. The complaint solely concerned off-label promotion which in the Panel's view meant that a product was licensed but its promotion was inconsistent with that licence. There was no evidence before the Panel that Boehringer Ingelheim had promoted Pradaxa outside the terms of its marketing authorization or in a manner inconsistent with the particulars listed in its summary of product characteristics and on this narrow ground no breach of the Code was ruled.

The Panel noted its rulings above and considered that Boehringer Ingelheim had not failed to maintain high standards and thus ruled no breach of the Code and consequently ruled no breach of Clause 2.

With regard to the complainant's comment about grants for medical research being discussed at medical symposia where prescribing information was available, the Panel considered that the complainant had not explained why such activity might be in breach of the Code. The complainant was non-contactable and so the Panel could not ask him/her for more information. A judgement had to be made on the evidence provided by the parties. The Panel noted Boehringer Ingelheim's submission that its corporate team had supported the congress organiser's Grants for Medical Research

Innovation and information relating to the grant was only shown at the end of Boehringer Ingelheim sponsored sessions, where the main information about the scientific research grant programme had been shared by the congress organiser itself. The agreement was neither dabigatran specific nor was dabigatran mentioned anywhere on the related documents. The Panel considered that the complainant had not demonstrated that, in displaying information about a medical research grant, Boehringer Ingelheim had breached the Code and the Panel thus ruled no breaches of the Code.

During its consideration of this case, the Panel noted that the fourth symposium presentation included claims for a specific reversal agent for dabigatran. The Panel was concerned that the medicine had thus been promoted prior to the grant of a marketing authorization which permitted its sale or supply and requested that Boehringer Ingelheim be advised of its concerns in this regard.

An anonymous, non-contactable complainant, who described him/herself as a UK health professional, complained about medical symposia at the European Society of Cardiology (ESC) Congress held in London 29 August – 2 September 2015. Boehringer Ingelheim marketed Pradaxa (dabigatran) which was a novel oral anticoagulant (NOAC).

COMPLAINT

The complainant asked for clarification on medical symposia. He/she understood that promotional presentations always went hand-in-hand with abbreviated prescribing information. However, a couple the complainant had attended had included discussions that were off-label and discussions about grants for medical research etc but the prescribing information was available and stated on the slides. The complainant did not think that having prescribing information available at a meeting made it promotional but he/she was confused about how to perceive such a meeting.

The complainant provided a copy of a Boehringer Ingelheim slide entitled 'Panel discussion and Q&A' from a symposium moderated by a US health professional. The slide stated 'Prescribing information is available at this meeting'.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to Clauses 3.1, 3.2, 9.1 and 2 of the 2015 Code. Boehringer Ingelheim was subsequently asked to comment on Clause 19 after it referred to this clause in its initial response.

RESPONSE

Boehringer Ingelheim stated that the details of the exact issue seemed unclear as the complainant appeared to be seeking clarity on the interpretation of the Code without reference to a specific presentation apart from a final Q&A slide. This made it difficult for Boehringer Ingelheim to respond, but it endeavoured to address what it interpreted as the substance of the apparent complaint.

The complainant had provided a photograph from the Boehringer Ingelheim sponsored satellite symposium held on Sunday, 31 August at the ESC Congress; the complainant had not detailed what he/she considered to be off-label and Boehringer Ingelheim strongly rejected any suggestion that it might have engaged in off-licence promotion during the sponsored symposium. Boehringer Ingelheim submitted that it conformed with Clauses 3.1 and 3.2 and had maintained high standards (Clause 9) and not brought the industry into disrepute (Clause 2).

The complainant also mentioned grants for medical research but provided no evidence to support the detail of this. For the purposes of clarity Boehringer Ingelheim dealt with the two issues separately.

1 Sponsored satellite symposium: Your patients, your practice, your choice: NOACs in the clinic

This was an hour long symposium organized and sponsored by Boehringer Ingelheim as part of a series of industry satellite symposia during ESC, offering delegates the opportunity to learn and exchange on the latest scientific information and developments from industry. Boehringer Ingelheim's sponsorship was made clear on all relevant materials, hence the reasoning for prescribing information being available.

The symposium comprised of four talks by speakers globally recognized for their expertise in anticoagulation and atrial fibrillation (AF), followed by a moderated Q&A (the photograph of the slide sent by the complainant). All topics were of interest to cardiologists in this disease area. Attendees at the ESC came from around the world, although there was a larger proportion from Europe. A link to the distribution of delegates' countries of origin published by the ESC was provided.

The first speaker provided an overview of the four currently licensed non vitamin K oral anticoagulants (NOACs); he also mentioned data from post-marketing sources and introduced the format and speakers for the remainder of the symposium (5 minutes).

The second presentation was about the management of patients on anticoagulation for AF who required ablation, an interventional procedure to help control the symptoms of atrial fibrillation. This was a topic under debate currently with a number of phase IV studies underway and was in line with the marketing authorization for Pradaxa in the UK and Europe (15 minutes).

The third speaker discussed the current challenges and decisions required in the management of AF

patients who required a coronary stent following an acute cardiac event. Again this was a widely debated topic given the challenges of both an interventional procedure and the requirement for additional antiplatelet therapy on top of anticoagulant therapy. Updated ESC guidelines on this topic were presented during another session at this meeting and the speaker sought permission to present this again in Boehringer Ingelheim's symposium. Again, a number of studies were running in this area, which like the second presentation was in line with the marketing authorization for Pradaxa in the UK and Europe (15 minutes).

The fourth and final speaker, relevant to the two previous talks, discussed the management of patients needing either elective or emergency surgery whilst receiving long-term anticoagulation. A patient case study was used to help communicate the current advice contained in the Pradaxa summary of product characteristics (SPC), as well as the risk management materials. Published data from sub-analyses of the RELY trial (phase III study for dabigatran in non-valvular atrial fibrillation) were also presented. The status of current developments in reversal agents was briefly discussed at the end of the session in order to provide fair, balanced and scientifically accurate content. All three reversal agents under current investigation, including Boehringer Ingelheim's specific reversal agent for dabigatran were presented and relevant slides contained a clear disclaimer that these were investigational compounds and not available for use in the EU in line with supplementary information to Clause 3. One slide was not used in the presentation as it had been prepared in case of FDA approval, so that the most up-to-date information could be provided should the situation change (15 minutes).

Boehringer Ingelheim submitted that the symposium focussed on the use of dabigatran in line with its marketing authorization and presented in a balanced, fair and accurate way. Boehringer Ingelheim believed that high standards had been maintained at all times.

2 Medical research grant

Boehringer Ingelheim submitted that the reference to the medical research grant was the support of an ESC research grant programme by Boehringer Ingelheim described below, although given the lack of specificity in the complaint it was difficult to be certain.

The corporate Boehringer Ingelheim cardiovascular team had financially supported a scientific programme developed by the ESC, entitled ESC Grants for Medical Research Innovation. The programme was covered by an agreement between Boehringer Ingelheim corporate and the ESC. A link to the programme outline on the ESC website was provided. It was neither dabigatran specific nor was dabigatran mentioned anywhere on the related documents. It was a specific condition of the programme that any applications seeking to investigate NOACs must include more than one NOAC.

Information relating to the grant was only shown at the end of Boehringer Ingelheim sponsored sessions at the ESC, where the main information

about the scientific research grant programme had been shared by the ESC itself. Boehringer Ingelheim submitted that the sponsorship of the research grant complied with the Code, in particular Clause 19.2 and took consideration of the supplementary information to Clause 19.1.

In conclusion, Boehringer Ingelheim submitted that the activities during the satellite symposium of 31 August 2015 and the research grant to the ESC were not in breach of Clauses 2, 3.1, 3.2, 9 or 19 of the Code.

Upon receipt of the response, the case preparation manager noted Boehringer Ingelheim referred to Clause 19 in its response. This was not raised initially but Boehringer Ingelheim was asked for any further comments.

Boehringer Ingelheim stated that the medical research grant was a global initiative between Boehringer Ingelheim (corporate) and the ESC. A copy of the contract with the financial details redacted for reasons of confidentiality was provided

The ESC was based in France and the research grant was governed by French law. The award of the grant therefore took place outside the UK. The eligibility for applying for the grant was global. This was not a grant made by or to a UK organisation and therefore potentially fell outside the scope of the Code.

Boehringer Ingelheim acknowledged, however, that the existence of the grant was advertised in the UK at the ESC meeting. The grant would in any case have complied with the requirements of Clause 19.2, if applicable, because it:

- was made to an association of health professionals and not to a health professional personally
- was made for the purpose of supporting research
- was documented and kept on record
- was not an inducement to prescribe, and
- would be publicly disclosed.

The recipient of the grant was the ESC, an association of health professionals with a stated mission to reduce the burden of cardiovascular disease in Europe. ESC's work included supporting research. The grant was not provided by Boehringer Ingelheim to any health professional personally. The purpose of the grant was to support four research projects in a number of cardiovascular areas. The research projects were selected by a scientific committee independently appointed by ESC. No research project in the UK was selected. The grant was documented and would be kept on record in accordance with Boehringer Ingelheim's normal records retention policy.

The provision of the financial support was very clearly non-promotional as indicated by section 1.1 of the contract:

'Any promotion for certain products or promotional language shall be avoided in the [Program]. Furthermore, the Grantee shall ensure

that no product advertisements or promotional materials will be published on the same web page as the [Program] content.'

This was further reinforced by Section 3.1:

'Boehringer Ingelheim and the Grantee agree and confirm that this Agreement has not been concluded in order to influence current or future sales transactions. The sponsoring does not commit the Grantee or its employees to accept or prefer services or products from Boehringer Ingelheim. Boehringer Ingelheim does not expect any preference for its products (Principle of Separation).'

Schedule 1 also clearly stated:

'Study proposals evaluating Non Vitamin K Anticoagulants (NOACs) must include more than one NOAC.'

This caveat was to avoid any possible link to Pradaxa.

A communication plan was included in the schedule outlining the ESC's role in announcing the grant programme. This was prepared and announced by the ESC. Boehringer Ingelheim used this same communication to announce the programme at the end of the scientific symposia held at the ESC meeting in 2015. Boehringer Ingelheim's role in supporting the grant programme was clearly disclosed and reference was made to the ESC web page.

As required by the supplementary guidance to Clause 19.2, the details of this grant would be publicly disclosed by Boehringer Ingelheim corporate in accordance with the EFPIA Disclosure Code.

PANEL RULING

The complainant was anonymous and non-contactable and so the Panel could not ask him/her for more information. As stated in the introduction to the Constitution and Procedure, anonymous complaints were accepted and like all complaints, judged on the evidence provided by the parties. A complainant had the burden of proving his/her complaint on the balance of probabilities. The Panel noted that the complainant had alleged that presentations he/she had attended included off-label discussions and discussions about grants for medical research. The complainant provided a copy of a Boehringer Ingelheim slide entitled 'Panel discussion and Q&A' from a symposium moderated by a US health professional. The slide stated 'Prescribing information is available at this meeting'.

The Panel noted Boehringer Ingelheim's submission that the slide provided by the complainant was from a Boehringer Ingelheim sponsored satellite symposium entitled 'Your patients, your practice, your choice: NOACs in the clinic'. The symposium comprised four presentations; 'Beyond the trials: NOACs in practice'; 'Your patient requires AF ablation: what would you do?'; 'Your patient with NVAf requires a coronary stent: what would you do?'; and 'Your patient requires surgery: what

would you do?'. The Panel noted that the focus of all four presentations was on the use of dabigatran as submitted by Boehringer Ingelheim. The complainant had not provided details of what he/she considered to be off-label. Conversely, Boehringer Ingelheim provided copies of all of the presentations and submitted that the topics of two presentations were currently under debate and a number of studies were ongoing in the areas but both topics were in line with dabigatran's marketing authorization. Whilst Boehringer Ingelheim submitted that the fourth presentation referred to its reversal agent for dabigatran which did not have an EU licence the Panel noted it did not have a complaint in this regard. The complaint solely concerned off-label promotion which in the Panel's view meant that a product was licensed but its promotion was inconsistent with that licence. There was no evidence before the Panel that Boehringer Ingelheim had promoted Pradaxa outside the terms of its marketing authorization or in a manner inconsistent with the particulars listed in its SPC contrary to Clause 3.2 and on this narrow ground no breach of that Clause was ruled.

The Panel noted that Boehringer Ingelheim had been asked by the case preparation manager to respond in relation to the requirements of Clause 3.1 which required that a medicine must not be promoted prior to the grant of the marketing authorization which permitted its sale or supply. As in the Panel's view the complainant had not alleged that an unlicensed medicine had been promoted, the Panel was obliged to rule no breach of Clause 3.1.

The Panel noted its rulings above and considered that Boehringer Ingelheim had not failed to maintain high standards and thus ruled no breach of Clause 9.1 and consequently ruled no breach of Clause 2.

With regard to the complainant's comment about grants for medical research being discussed at medical symposia where prescribing information was available, the Panel considered that the complainant had not explained why such activity might be in breach of the Code. The complainant was anonymous and non-contactable and so the Panel could not ask him/her for more information. A judgement had to be made on the evidence provided by the parties. The Panel noted Boehringer Ingelheim's submission that its corporate team had supported the ESC Grants for Medical Research Innovation and information relating to the grant was only shown at the end of Boehringer Ingelheim sponsored sessions at the ESC, where the main information about the scientific

research grant programme had been shared by the ESC itself. The agreement was neither dabigatran specific nor was dabigatran mentioned anywhere on the related documents. The Panel considered that the complainant had not demonstrated that in displaying information about a medical research grant Boehringer Ingelheim had breached the Code and the Panel thus ruled no breaches of Clauses 19.1, 9.1 and 2 accordingly.

During its consideration of this case, the Panel noted that the Boehringer Ingelheim satellite symposium was promotional and within that context the fourth presentation discussed the management of patients needing either elective or emergency surgery whilst receiving long-term anticoagulation and discussed the status of current developments in reversal agents. The Panel noted Boehringer Ingelheim's submission that all three reversal agents currently under investigation, including Boehringer Ingelheim's specific reversal agent for dabigatran, were presented and relevant slides contained a clear disclaimer that these were investigational compounds and not available for use in the EU in line with supplementary information to Clause 3 of the Code. The Panel assumed that the supplementary information referred to by Boehringer Ingelheim was that to do with the promotion of medicines at international meetings held in the UK when such medicines did not have a marketing authorization in the UK although they were authorized in another major industrialised country. It appeared that Boehringer Ingelheim's medicine was not licensed for use anywhere in the world and so it could not be promoted. The Panel noted that the final presentation in a promotional symposium had referred to the unlicensed medicine and included a slide which stated that it had a binding affinity ~ 350 times higher than dabigatran for thrombin, no procoagulant or anticoagulant effects expected, onset of action within 1 minute and a short half-life. The Panel noted that, as stated above, the complainant had not alleged that an unlicensed medicine had been promoted at the meeting. The Panel was concerned that the slide promoted the unlicensed medicine prior to the grant of a marketing authorization which permitted its sale or supply and requested that Boehringer Ingelheim be advised of its concerns in this regard.

Complaint received	21 December 2015
Case completed	8 February 2016

CLINICAL COMMISSIONING GROUP EMPLOYEE v PFIZER

Email about a webinar

A head of medicines and prescribing at a clinical commissioning group (CCG), complained about an email sent by a third party event organiser to another member of staff at the CCG.

The email was headed 'Don't miss the webinar. Understanding the Clinical and Practical Aspects for the Self-Administration of Sayana Press (medroxyprogesterone acetate)'. Details of the speakers (faculty) were named; a medical employee from Pfizer UK, a general practitioner with a special interest in gynaecology who was also a member of women's health forum and a nurse consultant in sexual health services. Details of the agenda followed and what appeared to be a separate advertisement for Sayana Press. The invitation concluded 'Thank you for your kind attention' followed by the Pfizer logo and prescribing information.

The complainant did not believe that the recipient of the email would have signed up to receive promotional material from Pfizer, therefore the email should not have been sent without prior consent. On closer inspection, the webinar seemed to be nothing more than a thinly disguised promotional event to increase the use of Sayana Press.

The complainant stated that whilst the manufacturer's name was clearly listed just above the prescribing information at the end of the 'webinar' information, the words 'this webinar is sponsored by' did not appear anywhere in the communication. The complainant thought such information needed to be explicit. The use of a third party event organiser to circulate the invitation together with the use of the word 'faculty' was alleged to be a cynical attempt to confer unwarranted educational authority to a purely promotional event and to circumvent the Code.

The detailed response from Pfizer is given below.

The Panel noted Pfizer's submission that the recipient had agreed to receive emails. The opt-in statement was clear that details of pharmaceutical company promotional meetings might also be sent. The Panel considered that prior permission had been obtained and no breach of the Code was ruled.

The Panel also ruled no breach of the Code as the limitation on frequency of mailings did not apply to emails as these could only be sent with prior permission.

In relation to the allegation of disguised promotion, the Panel considered that the recipient's initial impression was important. In the recipient's inbox the email appeared as from the sender and the third party and the subject heading was 'Understanding the Clinical

and Practical Aspects for the Self-Administration of Sayana Press (medroxyprogesterone acetate)'. On opening the email no indication was given in the heading that it was from a pharmaceutical company. The sender's address bore no apparent link to a pharmaceutical company. A reader had to scan down past the meeting details and what appeared to be an advertisement and claims before reaching the company name. The printed invitation was provided and the first mention of Pfizer was on page 3. The Panel considered that it was not sufficiently obvious at the outset that the email was a promotional email from a pharmaceutical company. The first part of the email gave very little indication of the nature of the meeting. In the Panel's view, the length of the email was such that the pharmaceutical company's involvement and that the email contained prescribing information would not appear until the recipient had scrolled down to the bottom of the email. Although a Pfizer employee was listed as being part of the faculty it was not sufficiently clear at the outset that both the email and the meeting were promotional. The Panel considered the promotional nature of the email was disguised and a breach of the Code was ruled.

The Panel also ruled a breach as the declaration of sponsorship was not sufficiently prominent to ensure that readers were aware of it at the outset.

A head of medicines and prescribing at a clinical commissioning group (CCG), complained about an email sent by a third party events organiser to another member of staff at the CCG.

The email was headed 'Don't miss the webinar. Understanding the Clinical and Practical Aspects for the Self-Administration of Sayana Press (medroxyprogesterone acetate)'. Details of the speakers (faculty) were named these being a Pfizer medical employee, a GP with special interest in gynaecology and a member of women's health forum and a nurse consultant in sexual health services. This was followed by details of the agenda and what appeared to be a separate advertisement for Sayana Press which was described as 'A convenient self-administered subcut LARC [long acting reversible contraceptive] that gives the "I-barely-have-a-moment" woman a choice'. The invitation concluded with 'Thank you for your kind attention. Pfizer Ltd' was followed by the Pfizer logo and prescribing information.

Sayana Press was indicated for long-term contraception and each subcutaneous injection provided contraception for at least 13 weeks.

COMPLAINT

The complainant alleged that the email was in breach of Clauses 11.2, 12 and 22 of the Code.

Clause 11.2 – Distribution of Promotion Material

The complainant did not believe that the recipient would have signed up to receive promotional material from Pfizer, but might have subscribed to receive information about relevant prescribing related educational events. The complainant did not think the webinar qualified as an educational event and therefore it should not have been sent to the recipient without her express prior consent.

Clause 12 – Disguised Promotion

The complainant stated that the email had been sent by a company which gave the impression of being involved in educational events. The event was called a 'webinar' and the term 'faculty' had been used to highlight some of the participants.

On closer inspection, it seemed to be nothing more than a thinly disguised promotional event to increase the use of Sayana Press – a product which was not even approved for use locally.

Clause 22 – Meetings, Hospitality and Sponsorship

The complainant referred to the supplementary information to Clause 22.4, Sponsorship and Reports of Meetings:

'Attention is drawn to Clause 9.10 which requires that all material relating to medicines and their uses, whether promotional or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company.'

The complainant stated that whilst the manufacturer's name was clearly listed just above the prescribing information at the end of the 'webinar' information, the words 'this webinar is sponsored by' did not appear anywhere in the communication. The complainant thought that any such information needed to be absolutely explicit. The use of a third party 'event organiser' to circulate the 'webinar' invitation together with the use of the word 'faculty' was alleged to be a cynical attempt to confer unwarranted educational authority to a purely promotional event and to circumvent the requirements of Clause 11.2.

When writing to Pfizer the Authority asked it to respond to Clauses 9.9 and 9.10 in addition to those clauses cited by the complainant (Clauses 11.2, 12.1 and 22.4).

The clauses cited by the complainant and the Authority were the same in the 2016 Code as in the 2015 Code and thus the Panel referred to the 2016 Code.

RESPONSE

Pfizer stated that the purpose of the live webinar was to educate health professionals and other relevant decision makers with an interest in women's health on the use of Sayana Press. Presentations were delivered by expert clinicians in sexual health who also advised on the use of the product and the selection of appropriate patients

for self-administration. There was a question and answer session followed by a brief summary of key learnings from the webinar.

The recipient's email address was registered on the women's health forum database. The database contained the following opt-in statements which were ticked by the recipient:

'Please tick if you would like to receive information about future events or medical education from [the forum].

Please tick if you would like to receive information from our partners this may include relevant promotional meetings run by pharmaceutical companies.'

Pfizer stated that neither of the above statements were pre-ticked, they were proactive opt-in statements which were very clear and must be completed in order to opt-in.

Both the third party and the forum had separate databases. For the purposes of the Sayana Press live webinar, the two parties agreed on a combined database to manage the subscriptions. Therefore upon registration to the forum database, the recipient's email address was added to the distribution to receive the invitation to the live webinar. The address was removed from the combined database and the forum database after the unsubscribe request was received in early January 2016.

Pfizer stated that the decision to combine databases was made by the forum and third party. It was important to highlight that the forum's permission wording (ticked by the recipient) expressly allowed for personal data to be shared with forum's partners (which would include organisations such as the third party) in relation to promotional events. By ticking the box, the individual provided consent for his/her information to be passed to organisers of promotional events.

Clauses 9.9 and 11.2 – prior permission of recipient; distribution of promotional material

Pfizer stated that the email invitation was distributed by the third party in December 2015 and a reminder email was sent in January 2016, to invitees who had given their permissions.

Pfizer submitted that there was no breach of Clause 9.9 because there was a valid permission, and no breach of Clause 11.2 which it submitted applied to mailings and not to emails provided there was prior consent which there was in this case.

Clause 12.1 – Disguised promotion

Pfizer stated that the email invitation sent for the webinar showed that the content was promotional. There was no attempt to disguise it as a non-promotional event. Sayana Press was a branded pharmaceutical product and was clearly advertised throughout the invitation. There was a Pfizer speaker on the agenda and a prominent Pfizer logo

underneath 'Pfizer Ltd' indicating that it was a Pfizer sponsored event. Further, there was prescribing information on the invitation as required for promotional content, together with the adverse event reporting statement, date of preparation and unique reference number. Pfizer therefore denied a breach of Clause 12.1.

Clauses 9.10 and 22.4 – Declaration of sponsorship

Pfizer acknowledged that whilst the invitation did not specifically state the exact nature of Pfizer's sponsorship, there was no attempt to disguise the event sponsor as could be seen from the clear inclusion of the Pfizer logo underneath 'Pfizer Ltd'. Given the addition of all the mandatory requirements for promotional material as described above, Pfizer submitted that it was clear that it was a Pfizer sponsored promotional webinar about its branded medicine Sayana Press and therefore did not breach Clauses 9.10 or 22.4.

For the reasons detailed above Pfizer submitted it was not in breach of Clauses 9.9, 9.10, 11.2, 12.1 or 22.4 of the Code.

PANEL RULING

The Panel noted Pfizer's submission that the recipient of the email had agreed to receiving emails from partners of the forum's database. The third party, which sent the email in question was one of these partners. The opt-in statement was clear that details of pharmaceutical company promotional meetings might also be sent. The Panel considered that prior permission had been obtained and no breach of Clause 9.9 was ruled.

The Panel noted that Clause 11.2 referred to the frequency of distribution and the volume of promotional material distributed. The supplementary information was clear that the limitations on frequency of mailings did not apply to emails as these could only be sent with prior permission. The Panel noted its ruling of no breach of Clause 9.9 above. The Panel therefore ruled no breach of Clause 11.2.

The Panel noted the supplementary information to Clause 12.1 referred to emails including that they must not give the impression that they were non-

promotional and the identity of the responsible pharmaceutical company must be obvious. The supplementary information to Clause 9.1 included that declarations of sponsorship must be sufficiently prominent to ensure readers were aware of such sponsorship at the outset. In this regard, the Panel considered that the recipient's initial impression of the email was important. In the recipient's inbox the email appeared as from the name of the sender and the third party and the subject heading was 'Understanding the Clinical and Practical Aspects for the Self-Administration of Sayana Press (medroxyprogesterone acetate)'. On opening the email no indication was given in the heading that it was from a pharmaceutical company. The sender's address bore no apparent link to a pharmaceutical company. A reader had to scan down past the meeting details and what appeared to be an advertisement and claims before reaching the company name, Pfizer. The printed invitation was provided with the certificate and the first mention of the company name was on page 3. The Panel considered that it was not sufficiently obvious at the outset that the email was promotional and from a pharmaceutical company. The first part of the email gave very little indication of the nature of the meeting. In the Panel's view, the length of the email was such that the pharmaceutical company's involvement and that the email contained prescribing information would not appear until the recipient had scrolled down to the bottom of the email. Although a Pfizer employee was listed as being part of the faculty it was not sufficiently clear at the outset from what would be the first screen that both the email and the meeting were promotional. The Panel considered the promotional nature of the email was disguised and a breach of Clause 12.1 was ruled.

The Panel also ruled a breach of Clause 22.4 as the declaration of sponsorship was not sufficiently prominent to ensure that readers were aware of it at the outset. It decided that its ruling of a breach of Clause 22.4 covered the alleged breach of Clause 9.10 and decided not to make a separate ruling in that regard.

Complaint received **5 January 2016**

Case completed **19 February 2016**

GENERAL PRACTITIONER v OTSUKA

Jinarc patient materials

A general practitioner alleged that Jinarc (tolvaptan) patient support materials, issued by Otsuka, portrayed the medicine as a treatment for autosomal dominant polycystic kidney disease (ADPKD) which constituted advertising to the public and ran the risk of raising patients' hopes and expectations. Jinarc was indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.

The detailed response from Otsuka is given below.

The Panel noted the complainant had not provided any materials or explained why, in his/her view, the patient literature described Jinarc as a treatment for ADPKD, advertised it to the public or risked raising patients' hopes and expectations. The complainant had not responded to a request for more information. The patient materials provided by Otsuka were a patient alert card, a patient/carer brochure, a user guide for a patient support line and a PDF and link to a disease awareness website for the public and health professionals. The Panel noted Otsuka's submission that the alert card and brochure were part of the risk management plan materials as agreed with the regulatory authorities and would be given by a health professional to patients prescribed Jinarc.

In the Panel's view the complaint included an allegation that the materials in question stated or implied that ADPKD could be cured. The patient alert card was clearly labelled as such and contained brief safety advice and referred in particular to adverse effects on the liver and to the severe dehydration that could occur with Jinarc. The brochure was entitled 'Jinarc (tolvaptan) Patient/carer education brochure'. The section which outlined the purpose of the brochure made the intended audience clear: 'for people with [ADPKD] who are being treated with Jinarc'. The brochure explained what Jinarc was, what it was used for etc and in answer to the question 'What is Jinarc' it was stated, *inter alia*, that Jinarc 'can slow down the growth of kidney cysts'. It was not stated or implied that Jinarc would stop the cysts from growing or otherwise cure the condition. The user guide was headed 'Otsuka Patient Support Service'; it was stated that the information therein was to help patients or their family members understand the service they would receive, how the service operated and how Otsuka would work with the hospital to help the patient. The open access disease awareness website had sections clearly marked for either health professionals or patients. According to the home page of the patient section, the website offered information, advice and support for ADPKD patients and their families or friends. One web page clearly stated 'There is no cure for ADPKD, but support from my family and doctor makes

life a lot easier'. In a section of the website about managing chronic conditions it was stated that there was currently no cure for ADPKD. The patient section of the website did not refer to Jinarc.

The Panel noted that the patient alert card and brochure were part of the product's risk management plan and provided to patients prescribed Jinarc by health professionals. The Panel considered that these items were factual and discussed the product in a non-promotional context. The Panel noted its comments on the user guide and patient section of the disease awareness website above. The Panel did not consider that any of the patient materials promoted Jinarc to the public as alleged. No breach of the Code was ruled. The Panel could find no evidence that Otsuka had described Jinarc as a cure for ADPKD or implied that it was such. In that regard the Panel did not consider that the material raised unfounded hopes of successful treatment as alleged. No breach of the Code was ruled.

The Panel noted its rulings above and considered that Otsuka had not failed to maintain high standards and thus ruled no breaches of the Code including Clause 2.

A general practitioner, complained about Jinarc (tolvaptan) patient support materials issued by Otsuka Pharmaceuticals (UK) Ltd. Jinarc was indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.

COMPLAINT

The complainant alleged that Jinarc was being portrayed as a treatment for ADPKD in patient literature which constituted advertising to the public and ran the risk of raising patients' hopes and expectations.

The case preparation manager asked the complainant to provide more information about the materials in question but did not receive a response.

When writing to Otsuka, the Authority asked it to consider the requirements of Clauses 2, 9.1, 26.1 and 26.2 of the 2016 Code.

RESPONSE

Otsuka noted that the complainant had not referred to any specific materials or activities and therefore it was unable to properly assess the merits of the complaint or respond meaningfully. Otsuka reserved full comment until such time as further information was provided by the complainant as requested by the Authority.

Otsuka stated that an enquiry into its activities relating to Jinarc did not reveal any activities or materials that could be considered in breach of Clauses 26.1, 26.2, 9.1, 2 or any other clause.

In response to a request for further information from the case preparation manager, Otsuka provided copies of its patient materials relating to Jinarc as follows:

- patient alert card (ref OPUK/0315/JIN/1091d) and patient brochure (ref OPUK/0315/JIN/1091c) distributed by health professionals to Jinarc patients as part of the risk management plan materials agreed with the regulatory authorities
- user guide for a patient support line (ref OPUK/0116/JIN/1032) distributed by health professionals to Jinarc patients to provide an overview of the patient support line provided by a third party on behalf of Otsuka
- disease awareness website (ref OPUK/0115/GEN/1010) developed for health professionals and the public. A link to the website and pdf of the content of the public area were provided.

PANEL RULING

The Panel noted that Clause 26.1 prohibited the advertising of prescription only medicines to the public. Clause 26.2 permitted information to be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or mislead with respect to the safety of the product and statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine. The Panel noted that companies could provide health professionals with material concerning a medicine with a view to its provision to patients to whom the medicine had already been prescribed as long as such material was factual and non-promotional and clearly stated the intended audience.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities; all complaints were judged on the evidence provided by the parties. The complainant in this case had not provided any materials or explained why, in his/her view, the Jinarc patient literature described the medicine as a treatment for ADPKD, advertised it to the public or risked raising patients' hopes and expectations. The complainant had not responded to the case preparation manager's request for more information. The patient materials provided by Otsuka were a patient alert card, a patient/carer brochure, a user guide for a patient support line and a PDF and link to a disease awareness website for the public and health professionals. The Panel noted Otsuka's submission that the alert card and brochure were part of the risk management plan materials agreed with the regulatory authorities and would be given by a health professional to patients prescribed Jinarc.

In the Panel's view the complaint included an allegation that the materials in question stated or implied that ADPKD could be cured.

The patient alert card was clearly labelled as such and contained brief safety advice and referred in particular to adverse effects on the liver and to the severe dehydration that could occur with Jinarc. The brochure was entitled 'Jinarc (tolvaptan) Patient/carer education brochure'. The section which outlined the purpose of the brochure made the intended audience clear: 'for people with [ADPKD] who are being treated with Jinarc'. The brochure explained what Jinarc was, what it was used for and how it should be used; it provided safety information and set out potential side-effects and what to do if they occurred. In answer to the question 'What is Jinarc' it was stated, *inter alia*, that Jinarc 'can slow down the growth of kidney cysts'. It was not stated or implied that Jinarc would stop the cysts from growing or otherwise cure the condition. The user guide was headed 'Otsuka Patient Support Service'; it was stated that the information therein was to help patients or their family members understand the service they would receive, how the service operated and how Otsuka would work with the hospital to help the patient. The website was an open access disease awareness resource with sections clearly marked for either health professionals or patients. According to the home page of the patient section, the website offered information, advice and support for ADPKD patients and their families or friends. There were sections entitled 'About ADPKD', 'ADPKD and you' and 'Managing ADPKD'. One web page clearly stated 'There is no cure for ADPKD, but support from my family and doctor makes life a lot easier'. In a section of the website about managing chronic conditions it was stated that there was currently no cure for ADPKD and that treatment focussed on managing symptoms and maintaining a healthy lifestyle. The patient section of the website did not refer to Jinarc.

The Panel noted that the patient alert card and brochure were part of the product's risk management plan and provided to patients prescribed Jinarc by health professionals. The Panel considered that these items were factual and discussed the product in a non-promotional context. The Panel noted its comments on the user guide and patient section of the disease awareness website above. The Panel did not consider that any of the patient materials promoted Jinarc to the public as alleged. No breach of Clause 26.1 was ruled. The Panel could find no evidence that Otsuka had described Jinarc as a cure for ADPKD or implied that it was such. In that regard the Panel did not consider that the material before it raised unfounded hopes of successful treatment as alleged. No breach of Clause 26.2 was ruled.

The Panel noted its rulings above and considered that Otsuka had not failed to maintain high standards and thus ruled no breach of Clause 9.1 and consequently ruled no breach of Clause 2.

Complaint received	3 February 2016
Case completed	23 March 2016

VOLUNTARY ADMISSION BY SANOFI GENZYME

Inappropriate hospitality

Sanofi Genzyme voluntarily admitted that it invited members of patient organisations to the Biotech Industry Association's (BIA) gala dinner in 2014 and 2015 and provided hospitality where there was no scientific meeting, promotional meeting, scientific congress or training. In addition, the subsistence exceeded £75 per person excluding VAT and gratuities.

In accordance with Paragraph 5.6 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority, the Director treated the matter as a complaint.

The detailed response from Sanofi Genzyme is given below.

The Panel noted that the BIA's gala dinners were not meetings organised for health professionals, other relevant decision makers (ORDM) or patient associations *per se*. However each company that attended could invite guests of their choosing and in that sense the Panel considered that each company's involvement had to be judged on its own merits. The Panel noted that Sanofi Genzyme's involvement in the gala dinners in 2014 and 2015 was such that it came within the scope of the Code. The Panel noted that Sanofi Genzyme referred to taking members of patient associations to the gala dinner in the years prior to 2014 but no specific details were provided.

The Panel was unsure about all the arrangements for the gala dinners. It only had the limited information provided by Sanofi Genzyme. It appeared that the event was attended by senior figures in the industry, government and the media. It appeared that speeches were given by the BIA's Chairman, chief executive officer (CEO) and others. Some attendees were possibly invited by the trade association and others by companies. There appeared to be a social element to the occasion. The Panel noted there would be some professional benefit in attending the BIA gala dinner and considered that although it was an important event with an opportunity for networking etc, it could not be described as having a clear educational content with hospitality secondary to the main purpose as required by the Code. The venue was prestigious and the level of hospitality was significant.

The Panel noted that in 2014 Sanofi Genzyme had taken a table at the gala dinner. Three Sanofi Genzyme employees attended together with seven people from various patient organisations as its guests. Accommodation and travel had been paid for at least one attendee. The Panel noted that the cost of each gala dinner ticket in 2014 was £425 plus VAT. Accommodation was paid for at least one attendee at £160. The Sanofi Genzyme submission implied it had paid for accommodation for all patient organisation attendees. The gala dinner

in 2014 was covered by the Second 2012 Code as amended. The Panel considered that by inviting only patient organisation members, Sanofi Genzyme's involvement in the 2014 dinner was such that it had organised a meeting for patient organisations and a breach of the Code was ruled.

The Panel noted that in 2015 Sanofi Genzyme had taken a table of ten. It appeared that it only had five spaces filled all of which appeared to be company employees. The list provided showed that seven people attended from Genzyme and Sanofi. One guest was from a technology organisation and the other two guests were from patient organisations. The Panel noted Sanofi Genzyme's submission that the arrangements for the two patient organisation members attending the 2015 dinner were last minute verbal invitations. The Panel noted that the cost of the tickets in 2015 was £450 plus VAT and accommodation was provided for the two patient organisation attendees at £149.99 per attendee. Although not all Sanofi Genzyme's guests were from patient associations the Panel considered that inviting one person who was not from a patient organisation did not mean that the company had organised a corporate meeting rather than one for patient organisations.

The gala dinner in 2015 was covered by the 2014 Code. The Panel therefore ruled a breach of the Code in relation to Sanofi Genzyme's involvement in inviting patient organisations to the dinner in 2015. The Panel noted that although the cost of the food and drink was not provided given the increase in ticket price to £450 and the nature of the subsistence, it was very likely that this would cost more than £75 plus VAT and gratuities and a breach of the Code was ruled as acknowledged by Sanofi Genzyme.

Sanofi Genzyme made a voluntary admission of a number of breaches of the Code relating to the same matter which had just come to its attention.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint the matter was taken up with Sanofi Genzyme.

COMPLAINT

Sanofi Genzyme stated that in January 2015 the company invited two members of patient associations to join it for a gala dinner which was organised by the Biotech Industries Association (BIA) and held in January 2015. Hospitality included tickets to the dinner and overnight accommodation.

Accordingly, Sanofi Genzyme submitted that its actions breached Clause 22.1 because it provided hospitality where there was no scientific meeting,

promotional meeting, scientific congress or training. In addition, it breached Clause 22.2 as the subsistence exceeded £75 per person excluding VAT and gratuities.

Sanofi Genzyme would disclose these transfers of value in its disclosure for 2015.

Sanofi Genzyme also voluntarily admitted that it took members of patient organisations to the BIA's gala dinner in 2014 and previous years in breach of the Code. That hospitality was disclosed in its aggregated disclosure of payments made for 2013 and 2014.

Sanofi Genzyme attended the gala dinner in January 2016. However, it did not invite any members of patient associations and it was very clear that it should not and would not invite patient association members to such events in future.

This matter was discussed with the company by those carrying out the audit of Sanofi Genzyme on 9 February 2016.

The case preparation manager pointed out that given the transition arrangements, the January 2015 BIA dinner would come within the scope of the 2014 Code and so although Sanofi Genzyme cited Clauses 22.1 and 22.2 of the 2015 Code, the relevant clauses of the 2014 Code would be 19.1 and 19.2. Sanofi Genzyme also referred to taking members of patient associations to the gala dinner in 2014 and 2013. These activities would have been covered by Clause 19.1 of the Second 2012 Edition of the Code. There was no stated upper limit for hospitality in that Code although, as now, it was stated that the costs involved must not exceed the level which recipients would normally adopt when paying for themselves.

Sanofi Genzyme was asked to provide the PMCPA with any further comments in relation to the requirements of Clauses 19.1 and 19.2 of the 2014 Code and Clause 19.1 of the Second 2012 Edition of the Code.

RESPONSE

Sanofi Genzyme provided copies of the job bags approving the invitations to the gala dinner in 2014 – it did not have job bags for 2015 as the members of the patient associations were invited at the last minute verbally and did not go through its electronic approval system. Emails confirming attendance at the 2015 gala dinner following a verbal invitation together with hotel invoices were provided. Material describing the event, a table plan for 2015, the invoice and the Sanofi Genzyme attendance list for 2016 which did not include members of any patient organisations were provided. Finally, Sanofi Genzyme provided a copy of its new standard operating procedure (SOP) which required all activities with patient organisations to be reviewed for compliance with the Code.

Sanofi Genzyme submitted that the gala dinner cost £450 per head. In addition, it paid for the members of the patient association's overnight accommodation which in 2015 cost £149.99 for each guest.

In relation to the clauses cited by the case preparation manager, Clauses 19.1 and 19.2 of the 2014 Code in respect of the gala dinner in 2015 and Clause 19.1 of the 2012 Code in respect of the gala dinner in 2013 and 2014, Sanofi Genzyme submitted that it had breached the Code by inviting members of patient organisations to such an event.

The company now had clear policies in place. It did not take members of patient organisations to the BIA's gala dinner in 2016 and had decided to stop attending the gala dinner going forward.

In 2015 Sanofi Genzyme paid for two patient associations to attend the gala dinner. Accommodation and travel was paid for two attendees. It appeared that one other patient association had been invited but did not attend.

The gala dinner 2015 was described in an email as a prestigious black tie event at the National History Museum. There was a champagne and canapé reception in the Darwin Centre where guests could meet, network and enjoy 'fabulous surroundings'. This was followed by 'a delicious four course meal' in the Hintze Hall (formerly Central Hall), 'the home of the famous diplodocus skeleton'. There was an opportunity for further networking after the meal at a bar until midnight. The cost for a table of ten was £4,250, the same as 2014, for early bookers. Individual tickets in 2014 and 2015 were £295 plus VAT. The cost for 2015 increased to £325 plus VAT after 1 September 2014. The first increase since 2008.

In response to a request for further information Sanofi Genzyme confirmed that the verbal invitations for 2015 were because it had not originally intended to invite guests from patient associations but as a few places became available the company decided to invite them.

The 2014 gala dinner was described as 'the flagship BIA Gala Dinner continues to be the premier bioscience networking event of the year' and the 2013 dinner was a chance to network with biotech companies, government and the media to meet old friends and make new business contacts. The evening started with champagne and canapés followed by a splendid four course meal in the magnificent Central Hall. There were speeches from the BIA's chief executive officer (CEO) and the chosen charity.

PANEL RULING

The Panel noted that the provisions of Clause 19 of the 2014 Code and the Second 2012 Edition of the Code applied to meetings organised for health professionals regardless of whether the meetings were promotional or not. Clause 19.1 of the 2014 Code and the Second 2012 Edition permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs incurred must not exceed the level which recipients

would normally adopt if paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff. The supplementary information stated that the impression created by the arrangements must be borne in mind. Meetings organised for groups of doctors, other health professionals and/or administrative staff which were wholly or mainly of a social or sporting nature were unacceptable. The supplementary information also stated that the requirements of the Code did not apply to the provision of hospitality other than to those referred to in Clauses 19.1 and 24.2 and the supplementary information to Clauses 20 and 23.2. Clause 24.2 stated that the requirements of Clause 19, which covered meetings for health professionals and appropriate administrative staff, also applied to pharmaceutical companies supporting patient organisation meetings.

In addition, Clause 19.2 of the 2014 Code stated that the cost of a meal (including drinks) provided by way of subsistence must not exceed £75 per person excluding VAT and gratuities. The supplementary information to Clause 19.2 stated that the maximum of £75 plus VAT and gratuities was appropriate only in very exceptional circumstances, such as a dinner at a residential meeting for senior consultants or a dinner at a learned society conference with substantial educational content. The cost of a meal (including drinks) should normally be well below this figure. The requirements relating to hospitality in Clause 19.1 and its supplementary information applied in this case.

The Panel noted a previous case, Case AUTH/1604/7/04, which included a voluntary admission by a company in relation to its invitation to health professionals to attend the ABPI Annual Dinner in 2004 as guests of the company. Whilst noting that there had been substantial changes to the arrangements for the ABPI Annual Dinner since that time, the Panel considered that this previous case had some relevance to the case now before it. There had also been changes to the ABPI Code since then including the introduction of the financial limit for subsistence.

Turning back to Case AUTH/2821/2/16, the Panel noted that the gala dinner was not a meeting organised for health professionals, other relevant decision makers (ORDM) or patient associations *per se*. However each company that attended could invite guests of their choosing and in that sense the Panel considered that each company's involvement had to be judged on its own merits. The Panel noted that Sanofi Genzyme's involvement in the gala dinner in 2014 and 2015 was such that it came within the scope of the Code. The Panel noted that Sanofi Genzyme referred to taking members of patient associations to the gala dinner in the years prior to 2014 but no specific details were provided.

The Panel was unsure about all the arrangements for the gala dinners. It only had the limited information provided by Sanofi Genzyme. It appeared that the event was attended by senior figures in the industry, government and the media. It appeared that speeches were given by the BIA's Chairman, chief

executive officer (CEO) and others. Some attendees were possibly invited by the trade association and others by companies. There appeared to be a social element to the occasion. The Panel noted there would be some professional benefit in attending the BIA's gala dinner and considered that although the gala dinner was an important event with an opportunity for networking etc, it could not be described as having a clear educational content with hospitality secondary to the main purpose as required by the Code. The venue was prestigious and the level of hospitality was significant.

2014 gala dinner

Sanofi Genzyme submitted details of the 2014 gala dinner. There were speeches from the BIA's Chairman, CEO, the Chancellor of the Exchequer and a charity.

The Panel noted that in 2014 Sanofi Genzyme had taken a table at the gala dinner. The general manager UK & Ireland, the medical director of Sanofi Genzyme, and the director of the multiple sclerosis business unit from Genzyme attended together with seven people from various patient organisations as its guests. Accommodation and travel had been paid for at least one attendee. The Panel noted that the gala dinner was a formal occasion; the cost of each ticket in 2014 was £425 plus VAT. Accommodation was paid for at least one attendee at £160. The Sanofi Genzyme submission implied it had paid for accommodation for all patient organisation attendees. The Panel considered that by inviting only patient organisation members, Sanofi Genzyme's involvement in the 2014 BIA dinner was such that it had organised a meeting for patient organisations. The Panel noted its general comments above.

The gala dinner in 2014 was covered by the Second 2012 Code as amended. The transition arrangements for the 2014 Code were such that newly introduced requirements did not apply during 1 January 2014 – 30 April 2014. As noted above Clause 19.1 in the Second 2012 Edition of the Code as amended was similar to the 2014 Code. The Second 2012 Code as amended did not limit the cost of subsistence. The Panel therefore ruled a breach of Clause 19.1 of the Second 2012 Code as amended in relation to Sanofi Genzyme's involvement in inviting patient organisations to the 2014 gala dinner.

2015 gala dinner

Sanofi Genzyme submitted details of the 2015 dinner although the material provided did not include a date. There were speeches from the BIA's CEO, the Minister for Life Sciences, the Chairman of the BIA and a charity.

The Panel noted that in 2015 Sanofi Genzyme had taken a table of ten. It appeared that it only had five spaces filled as of 15 January 2015 all of which appeared to be company employees. The list provided showed that seven people attended from Genzyme and Sanofi. One guest was from an international technology transfer organisation and the other two guests were from patient

organisations. The Panel noted Sanofi Genzyme's submission that the arrangements for the two patient organisation members attending the 2015 dinner were last minute verbal invitations. The Panel noted that the cost of the tickets in 2015 increased to £450 plus VAT and accommodation was provided for the two patient organisation attendees at £149.99 per attendee. Although not all Sanofi Genzyme's guests were from patient associations the Panel considered that inviting one person who was not from a patient organisation did not mean that the company had organised a corporate meeting rather than one for patient organisations. The Panel noted its general comments above.

The gala dinner in 2015 was covered by the 2014 Code. The Panel therefore ruled a breach of Clause 19.1 of the 2014 Code in relation to Sanofi Genzyme's involvement in inviting patient organisations to the dinner in 2015. The Panel noted that although the cost of the food and drink was not provided given the increase in ticket price to £450 and the nature of the subsistence, it was very likely that this would cost more than £75 plus VAT and gratuities. The Panel noted that Sanofi Genzyme

had admitted a breach of Clause 22.2 of the 2015/2016 Code in relation to the 2015 event on the basis that the subsistence exceeded £75 plus VAT. A breach of Clause 19.2 of the 2014 Code was thus ruled.

The Panel noted that the case preparation manager had not cited Clauses 9.1 and 2 for Sanofi Genzyme to consider. The Panel was thus unable to make a ruling on these clauses.

During its consideration of this case, the Panel noted Sanofi Genzyme's submission that the arrangements for attending the 2015 BIA dinner were last minute verbal invitations which did not go through the company's approval systems. The Panel noted that Clause 14.3 of the 2014 Code required that material related to working with patient organisations needed to be certified. It requested that its concerns were drawn to the attention of Sanofi Genzyme.

Complaint received **18 February 201**

Case completed **11 April 2016**

ANONYMOUS v CHIESI

Conduct of employees

The complainant, who wished to remain anonymous, alleged that a regional business manager (RBM) and an account executive, who had only been with Chiesi for five weeks, visited customers in a named location before they had been fully validated and compliant with their products. Both had previous experience in the industry but to go out and see customers before completing an initial training course should not be allowed.

The detailed response from Chiesi is given below.

The Panel noted that the Code required that representatives must be given adequate training and have sufficient scientific knowledge to enable them to provide full and accurate information about the medicines which they promoted. The Panel noted that Chiesi had provided copies of the validation score sheets from the initial training course (ITC) attended by the two new members of the field force in question. Delegates were validated on their knowledge of pharmacovigilance, the Code, NextHaler chronic obstructive pulmonary disease (COPD) summary of product characteristics (SPC), high strength Fostair and NextHaler SPC and three standard operating procedures (SOPs); there was a final validation on respiratory knowledge. The two employees passed all of the validations.

The Panel noted that the two new employees had had previous experience within the industry before joining Chiesi. Nonetheless, both had been included in the Chiesi ITC which ran for five weeks. The first two and last two weeks were spent at Chiesi head office and week three was field-based. ITC delegates had been verbally briefed not to undertake any promotion to customers during week three. The Panel noted Chiesi's detailed breakdown of the activities undertaken by the RBM and the account executive during that week; there was no evidence that either had promoted medicines to health professionals in the named location as alleged. The two new members of staff had been out on the territory on the final day of the field-based week but neither had been in the named location. There was an exchange at one practice in another location about a request for Chiesi placebo devices. The RBM acknowledged receipt of the request but stated, as per the verbal briefing which they had been given, that neither he/she nor his/her colleague could engage in conversation until they had completed their training. Another practice had discussed the types of meetings pharmaceutical companies could potentially support in the area. Chiesi submitted that there was no product promotion.

The Panel was concerned that ITC delegates were only verbally briefed about not promoting products during the field-based week given the importance of such instructions to compliance; written briefing would have been more helpful. The onus was on the complainant to prove his/her complaint on the balance of probabilities and the Panel considered

that there was no evidence to substantiate his/her allegations. The Panel considered that, on the balance of probabilities, the two employees had not promoted medicines to customers before they had passed the ITC. No breach of the Code was ruled. The Panel did not consider that high standards had not been maintained and so no breach was ruled. The Panel further ruled no breach of Clause 2.

A complainant who wished to remain anonymous, complained about two new employees of Chiesi Limited.

COMPLAINT

The complainant alleged that a regional business manager (RBM) and an account executive, who had only been with Chiesi for five weeks, visited customers in a named location before they had been fully validated and compliant with their products.

The complainant noted that both had previous experience in the industry but to go out and see customers before completing an initial training course should not be allowed.

When writing to Chiesi, the Authority asked it to consider the requirements of Clauses 2, 9.1, and 15.1 of the Code.

RESPONSE

Chiesi submitted that the RBM and account executive started with Chiesi in January 2016.

Both employees started the Chiesi initial training course (ITC) on 18 January 2016. The ITC was a 5-week programme and was structured as follows:

Week	Dates	Activity Detail	Location
1	18 – 22 January	ITC, including Pharmacovigilance validation	Head Office
2	25 – 29 January	ITC, including summary of product characteristics (SPC) & ABPI validations	Head Office
3	1 – 5 February	Shadow week (territory, team and customer orientation week)	Field Based
4	8 – 12 February	ITC, including selling skills	Head Office
5	15 – 19 February	ITC, including final examination & standard operating procedures (SOPs)	Head Office

Chiesi provided a copy of the formal ITC agenda.

Prior to the shadow week, the new employees were trained on product and respiratory disease knowledge, including product SPC training, pharmacovigilance and Code and formally validated via the Chiesi Learning Management Systems (LMS), an online training platform with built-in functionality to enable unique, randomised questions and tests to be completed by learners to assess and validate retention of learning knowledge. Both employees achieved the required pass marks. Chiesi provided copies of the supporting validations completed at the end of week two.

At the end of week two of the ITC, the trainer provided a full verbal brief on the purpose of the shadow week, the briefing covered the following points:

- Shadow week was an opportunity to consolidate learning by observing the conduct of others in surgery
- Provide the opportunity to develop relationships with the RBM and regional colleagues
- Instructions provided to delegates that they were not signed off to promote and were unable to engage or participate in any promotional/product discussion with any health professionals
- Delegates instructed that if they were asked a direct question about a product by a health professional, they must explain that they were in training and unable to comment
- Delegates instructed that if they were offered the opportunity to practise in call whilst shadowing an experienced account executive, they should refuse.

The RBM, the new account executive and the trainer confirmed that a detailed brief was provided and covered the purpose of the shadow week, along with the instructions not to participate in any promotional activity. The RBM and the account executive stated that they did not promote any product to a health professional during their shadow week.

After completing the shadow week, delegates returned to Chiesi head office to complete the ITC. Week four focused mainly on selling skills with the opportunity for delegates to undertake role play activity and to consolidate learning. At the start of week five, all delegates had to undertake an examination and role play validations in order to receive formal approval before undertaking any promotional activity. Chiesi provided a copy of the examination paper along with a summary of the results achieved.

During week five, the following SOPs were trained:

- UK-SOP-0247 Use of electronic communication by salesforce
- UK-SOP-0007 Procedure for the recall of promotional and non-promotional materials
- UK-SOP-0237 Materials distribution
- UK-SOP-0013 Meetings organised by field based personnel
- UK-SOP-0010 Sales procedure for handling on and off label requests for information
- UK-SOP-0225 Finance procedure for claiming business expenses.

For UK-SOP-0247, UK-SOP-0007, UK-SOP-0013 and UK-SOP-0010 delegates had to complete an electronic validation via the Chiesi LMS; they were not validated on UK-SOP-0237 and UK-SOP-0225 as these dealt solely with the internal Chiesi processes for completing expenses and ordering materials. Chiesi provided copies of the validation results and questions (where applicable), the SOPs and Guidance Notes.

Chiesi also provided copies of all the formal presentations delivered and additional material used during the ITC.

The investigation found that the slides 'CHRTD20120771 – Respiratory Disease & Asthma', were first certified in August 2012, were re-certified in July 2013 but had not been re-certified for use during the January 2016 ITC. The slides 'CHRTD20130890 – Asthma Management' were originally certified in August 2013, but had not been re-certified for use during the January 2016 ITC. Chiesi accepted that this was an error on its part and would ensure that it did not happen in the future. A medical signatory had reviewed the two sets of slides and confirmed that both were suitable for re-certification and would have been suitable for use during the January 2016 ITC.

The internal investigations found no evidence of any contact with customers in the named location as alleged. The RBM and the account executive confirmed they had not visited the named location during their ITC shadow week. Chiesi provided a breakdown of the activities covered during the shadow week for the two employees.

The 5 February was the only day on which both the new RBM and the new account executive were together during that week.

During the course of the orientation day on 5 February, the RBM showed the account executive how to navigate around the territory, calling in on surgeries to leave contact details and let them know that Chiesi had a new account executive. No product promotion occurred in any of the surgeries visited.

At one of the surgeries called upon (location named but not that named by the complainant) a nurse had asked for Chiesi placebo devices. The RBM informed the receptionist that a request had been received but would be fulfilled at a future date. During the course of this discussion, the nurse who made the request made herself known. The RBM acknowledged the nurse and repeated that the request had been received but they were unable to engage in a conversation until they had completed their training. The new account executive left his/her contact details.

On 5 February the only other direct contact the new RBM and the new account executive had with anyone other than reception staff, was with a practice manager (location named but not that named by the complainant) who provided an overview of the type of meetings the pharmaceutical industry could potentially support in the area. Chiesi submitted that there was no product promotion.

Both employees had over 20 years' experience working in the pharmaceutical industry and had passed the ABPI Examination.

Having fully investigated the complaint, Chiesi believed that a thorough training programme was provided to the new RBM and the account executive. Before starting the shadow week (week 3 of the ITC) the individuals received full training and completed validations on the Code, pharmacovigilance and product SPCs. A full verbal brief was provided by the trainer to all ITC delegates prior to the shadow week which confirmed that under no circumstances should any product promotion be conducted during the shadow week. No evidence was found during the course of the investigation that any product promotion was undertaken during the shadow week.

As demonstrated above, Chiesi strongly denied a breach of Clause 15.1 and that it had not failed to maintain high standards and accordingly had not reduced confidence in the industry or brought the industry into disrepute. It therefore followed that Chiesi denied that it was in breach of Clauses 9.1 or 2.

PANEL RULING

The Panel noted there had been no changes to Clauses 2, 9.1 and 15.1 of the 2015 Code and thus it considered this case in relation to the 2016 Code.

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. The complainant had not provided any evidence to substantiate the allegations made. The case preparation manager had acknowledged receipt of the complaint and reminded the complainant that all complaints were judged on the evidence provided by the parties. The complainant was asked to provide any additional information that he/she might have to support his/her case. None was received.

The Panel noted that Clause 15.1 stated that representatives must be given adequate training and have sufficient scientific knowledge to enable them to provide full and accurate information about the medicines which they promoted. The Panel noted that Chiesi had provided copies of the validation score sheets from the ITC attended by the two new members of the field force in question. The score sheets showed that delegates were validated on their knowledge of pharmacovigilance, the Code, NextHaler COPD (SPC), high strength Fostair and NextHaler (SPC) and three SOPs; there was a final 105 question validation on respiratory knowledge. The validation results showed that the two new employees passed all of the validations.

The Panel noted that the two new employees in question had had previous experience within the

industry before joining Chiesi. Nonetheless both had been included in the Chiesi ITC which started on 18 January; the course ran for five weeks and finished on 19 February. The first two and last two weeks were spent at Chiesi head office and week three was field-based. ITC delegates had been verbally briefed not to undertake any promotion to customers during week three. The Panel noted Chiesi's detailed breakdown of the activities undertaken by the RBM and the account executive during that week; there was no evidence that either had promoted medicines to health professionals in the location named by the complainant as alleged. The two new members of staff had been out on the account executive's new territory on the final day of the field-based week but neither had been in the named location. There was an exchange at one practice in another location about a request for Chiesi placebo devices. The RBM acknowledged receipt of the request but stated, as per the verbal briefing which they had been given, that neither he/she nor his/her colleague could engage in conversation until they had completed their training. A practice director in a third location had discussed the types of meetings pharmaceutical companies could potentially support in the area. Chiesi submitted that there was no product promotion.

The Panel was concerned that ITC delegates were only verbally briefed about not promoting products during the field-based week given the importance of such instructions to compliance; written briefing would have been more helpful. Nonetheless as noted above, the onus was on the complainant and the Panel considered that there was no evidence to substantiate his/her allegations. The Panel considered that, on the balance of probabilities, the two employees had not promoted medicines to customers before they had passed the ITC. No breach of Clause 15.1 was ruled. The Panel did not consider that high standards had not been maintained and so no breach of Clause 9.1 was ruled. The Panel noted its rulings of no breach of the Code and further ruled no breach of Clause 2.

During the consideration of this case, the Panel noted Chiesi's admission that two of the slide sets used on the ITC were last approved for use in mid 2013 – they had not been re-approved for use at the January/February 2016 ITC. The Panel noted that Chiesi had stated that it would ensure that such would not happen again. Nonetheless, the Panel requested that Chiesi be advised of its concerns in this regard particularly given the importance of certification to self regulation.

Complaint received	24 February 2016
Case completed	18 April 2016

CODE OF PRACTICE REVIEW – May 2016

Cases in which a breach of the Code was ruled are indexed in **bold type**.

AUTH/2721/7/14	Shire v Genzyme	Material for an advisory group	<p>Breach Clauses 2</p> <p>Four breaches Clause 3.2</p> <p>Twenty breaches Clause 7.2</p> <p>Eleven breaches Clause 7.3</p> <p>Six breaches Clause 7.4</p> <p>Two breaches Clause 7.6</p> <p>Five breaches Clause 7.8</p> <p>Breach Clause 7.10</p> <p>Two breaches Clause 8.1</p> <p>Breaches Clauses 9.1 and 14.1</p> <p>Required to issue corrective statement by the Appeal Board and two re-audits required by Appeal Board</p>	Appeal by respondent	Page 3
AUTH/2790/8/15	Anonymous, non-contactable ex-employee v Chugai	Consultancy arrangements	No breach, complaint should not have proceeded	Appeal by respondent	Page 52
AUTH/2793/9/15	Clinical Pharmacist v AstraZeneca	Identifying patients suitable for Forxiga treatment and failing to provide an accurate response to the Panel	<p>Breaches Clauses 3.2, 7.2, and 9.1</p> <p>Required to issue corrective statement and public reprimand by the Appeal Board</p>	Report from the Panel to the Appeal Board	Page 56
AUTH/2795/9/15	Anonymous, non-contactable NHS Whistle Blower v Napp	Promotion of Remsima	Breaches Clauses 9.1, 18.1 and 22.1	Appeal by respondent	Page 67
AUTH/2809/12/15	Genzyme v Amicus Therapeutics	Promotion of a medicine to a patient organisation	Breaches Clauses 3.2, 9.1, 14.1 and 14.3	Appeal by respondent	Page 83
AUTH/2812/12/15	Anonymous, non-contactable v Mylan	Exhibition stand design and hospitality	Breaches Clauses 9.1 and 22.1	No appeal	Page 93
AUTH/2814/12/15	Anonymous, non-contactable v Boehringer Ingelheim	Symposia at a meeting	No breach	No appeal	Page 95

AUTH/2818/1/16	Clinical Commissioning Group employee v Pfizer	Email about a webinar	Breaches Clauses 12.1 and 22.4	No appeal	Page 99
AUTH/2819/2/16	General Practitioner v Otsuka	Jinarc patient materials	No breach	No appeal	Page 102
AUTH/2821/2/16	Voluntary admission from Sanofi Genzyme	Inappropriate hospitality	Breaches Clauses 19.1 and 19.2	No appeal	Page 104
AUTH/2824/2/16	Anonymous v Chiesi	Conduct of employees	No breach	No appeal	Page 108

The Prescription Medicines Code of Practice Authority was established by the Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself. Compliance with the Code is obligatory for ABPI member companies and, in addition, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and other relevant decision makers and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including any printed or electronic material used by them
- the supply of samples
- the provision of inducements in connection with the promotion of medicines and inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems, social media and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- disclosure of transfers of value to health professionals and organisations
- joint working between the NHS and pharmaceutical companies

- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants, donations and benefits in kind to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of three of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member does not participate and is not present when the Panel considers it.

Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, must be in a majority when matters are considered by the Appeal Board.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Further information about the Authority and the Code can be found at www.pmcpa.org.uk

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria St, London SW1E 6QT

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.