

# GENZYME v SHIRE

## Use of a reprint

Genzyme Therapeutics complained about the use of a reprint from *The Lancet* (Mehta *et al* 2009) by Shire Pharmaceuticals to promote Replagal (agalsidase alfa). Replagal and Genzyme's product Fabrazyme (agalsidase beta) were both indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry's disease.

Genzyme knew that Shire had made a voluntary admission about the use of the reprint [Case AUTH/2590/3/13] but it was concerned that the company might not have included in that admission an adequate description of the breach of its undertaking given to Genzyme. Genzyme explained that in February 2010 Shire gave an undertaking not to deliberately refer to or use an unsubstantiated, misleading and incorrectly favourable bar chart from Mehta *et al* which compared Replagal with Fabrazyme. The bar chart was subsequently corrected in 'Department of Error' (Lancet 2010). However in December 2012 Shire reproduced the uncorrected bar chart in a promotional piece.

Genzyme stated that the withdrawal of the incorrect and misleading promotional article was an insufficient remedy because it had already requested that Shire stop using the incorrect material and Shire had already given a (qualified) undertaking to this effect. Furthermore the misleading information was in the public domain. Shire broke off inter-company dialogue on the matter stating that it would make a 'voluntary admission'. Genzyme did not consider this to be truly voluntary.

Genzyme explained that in 2009 Mehta *et al* was published in *The Lancet*. A bar chart in the paper depicted rates of decline of renal function in different populations of Fabry patients; this was quantified as decline of estimated glomerular filtration rate (eGFR) in millilitres/minute/year/body surface area (ml/min/year/1.73m<sup>2</sup>). Stratified populations from the study were reported, as well as references to populations from other studies. This appeared to have been done to provide comparison and context and included Fabrazyme data from a separate study.

The bar chart depicted the rate of decline in renal function to be about 2.8ml/min/year/1.73m<sup>2</sup> for Fabrazyme which was similar to the rates shown in males for Replagal. This was a serious error. The actual rate of decline of eGFR for Fabrazyme was about 1.1 ml/min/year/1.73m<sup>2</sup>, which was considerably better than both the incorrect rate shown in the original bar chart and the rates prominently displayed for Replagal. Genzyme alleged that the bar chart, therefore, showed an incorrectly favourable comparison between the products which was misleading and unsubstantiated.

Genzyme noted that Mehta *et al* stated: '[A named author] participated in database design, data

analysis and interpretation, writing, creation of figures, and study design'. No other author was credited with 'creation of figures'. The named author was a former Shire employee which Genzyme submitted demonstrated the clear provenance of the original error in the bar chart. A correction, published in *The Lancet Department of Error 2010*, gave the correct rates of decline of eGFR and clearly favoured Fabrazyme.

Consistent with Lancet policy, the original publication remained unaltered on *The Lancet* website meaning that, although linked electronically, the correction and the original publication were quite separate in the database. Whilst not ideal, Genzyme accepted this policy.

However, Genzyme was particularly concerned that the error came directly and solely from a Shire employee and Genzyme remained unsure of exactly how the very critical error arose. The error which disparaged the efficacy of Fabrazyme was clearly very important.

Genzyme pointed out to Shire in December 2009 the need for Shire to exercise appropriate professional care in directing parties to the article or using it in promotion. During this correspondence Genzyme's fears were exacerbated when it discovered a Shire press release drawing attention to the original article without mention of the correction.

Shire stated in a letter of 8 February 2010 to Genzyme that it '... will not deliberately refer to, or use [the bar chart] in its uncorrected form.

However, Shire and all of its affiliates ... reserve the right to use,

- the Article when accompanied by the correction notice;
- any data including the corrected [bar chart], and any other figures or tables from the Article, for any purpose(s) that Shire may deem to be appropriate in the future.'

While this was not 'unconditional' Genzyme concluded that since Shire knew about the error, and in accordance with the provisions of the Code, it would proscribe any use of the uncorrected bar chart in promotion or any other communication.

Genzyme was therefore very concerned when it discovered that Shire had distributed a promotional piece from its stand at a cardiology meeting in London, 2012. The material was one of a series collectively entitled 'The Replagal Reprint Collection' and was individually titled 'Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data'. A reprint of Mehta *et al* with the added published, corrected bar chart was included. However, the correction was

remote from the original incorrect bar chart. The uncorrected bar chart appeared in the main body of the text whereas the correction appeared in isolation, alone on the last page after the references. There was no reference to it from either the incorrect bar chart or elsewhere in the body of the text. It was unlikely that a reader would notice the correction and if they did, they would need to study both bar charts to understand its significance in terms of the comparison with Fabrazyme.

Genzyme alleged that the use of this reprint with the uncorrected bar chart constituted a comparison with Fabrazyme which was inaccurate and based on incorrect statistics, misleading and not capable of substantiation. Further, Genzyme alleged that Shire's use of this reprint without a clear reference to the corrected bar chart was in breach of its undertaking to Genzyme and in breach of Clause 2.

Genzyme stated that this failure to self-regulate and recognize the importance of both the Code and inter-company dialogue was so serious as to risk damaging the reputation and credibility of the industry and therefore Genzyme alleged a breach of Clause 2.

The detailed response from Shire is given below.

The Panel considered that the circumstances were unusual in that during inter-company debate, Shire had made a voluntary admission to the PMCPA (Case AUTH/2590/3/13). Shire had not provided Genzyme with the details of its voluntary admission and the case report was yet to be published. However the complaint to be considered was about the reprint folder used at a meeting on 19 November 2012. The folder contained a four page summary and the official Mehta *et al* reprint from The Lancet which included the corrected bar chart on the last page and was the same material as that which was the subject of the voluntary admission.

Firstly, the Panel noted its ruling in Case AUTH/2590/3/13:

The Panel noted the error in the bar chart. It also noted that Mehta *et al* did not compare Fabrazyme and Replagal in the text of their paper and once notified of the error, the lead author asked The Lancet to publish a corrected bar chart which it did. The official reprint of Mehta *et al* included the corrected bar chart on the last page; to see the corrected bar chart the reader would have to turn over the final page of the paper although the Panel noted that it was clear from the last page of the paper that something was printed on the reverse. The cover of the reprint referred the reader to The Lancet's website for WebExtra content. Once on The Lancet website, there was a link from Mehta *et al* to the corrected bar chart.

The Panel noted that Shire had distributed Mehta *et al* in a reprint folder together with a four page, A4 summary. The reprint folder front page cited both the references for the original paper and the corrected bar chart as did the front page of the A4 summary. The A4 summary gave

a brief overview of Mehta *et al* and made no comparisons with Fabrazyme; neither the original nor the corrected bar chart was included in the A4 summary.

The Panel considered that it was unfortunate that Mehta *et al* had published an incorrect bar chart. Nonetheless, the reprint distributed by Shire included the corrected bar chart, readers were directed to The Lancet website where there was a link to the corrected bar chart and the cover of the reprint carrier cited the reference for both the original paper and the corrected bar chart. Other than in the bar chart, the authors did not compare Replagal with Fabrazyme and the A4 summary of Mehta *et al* drew no comparisons between the two medicines. Taking all the circumstances into account the Panel did not consider that the material at issue was misleading. The Panel did not consider that there had been a failure to uphold high standards. No breaches of the Code were ruled.

Turning now to the case before it, Case AUTH/2593/4/13, the Panel noted Genzyme's allegation that the use of the reprint with the uncorrected bar chart constituted an inaccurate, misleading comparison based on incorrect statistics which was not capable of substantiation. The Panel considered that the reasons for its rulings of no breach of the Code in Case AUTH/2590/3/13 applied to the case now before it. The Panel did not consider that the material as a whole constituted a misleading comparison or was not capable of substantiation. The company had used the official Lancet reprint and had not referred to the Fabrazyme data in the A4 summary or the reprint carrier. The Panel considered that taking all the circumstances into account the material at issue was not in breach of the Code as alleged. Thus the Panel ruled no breaches of the Code.

The Panel noted Genzyme's allegations about the involvement of one of the authors who was a former Shire employee. Mehta *et al* stated under a heading 'contributors' that Shire's former employee participated in database design, data analysis and interpretation, writing, creation of figures and study design. The Panel did not know what 'participated' meant in this regard noting that Shire's former employee was the only author with 'creation of figures' listed. Genzyme alleged that the statement demonstrated the clear provenance of the original error although elsewhere in the complaint the company remained '... unsure exactly how the very critical error arose'. The Panel noted that the error in the bar chart had not been picked up in the review process which according to Shire included review by the authors, Shire and The Lancet. Shire submitted that it did not know of the error when Mehta *et al* was first published.

The Panel noted Shire had agreed with Genzyme a number of actions. Shire had also reserved the right to make certain use of the article and its correction. The outcome of inter-company dialogue was a matter for companies. A breach of inter-company commitments was not necessarily a breach of the Code. Such a commitment was not the same as

a formal undertaking given to the PMCPA by a company ruled in breach of the Code. The Panel noted its rulings above of no breach of the Code. It did not consider that Shire's use of the reprint, without a clear reference to the corrected bar chart, alleged to be in breach of Shire's agreement with Genzyme, amounted to a breach of Clause 2 as alleged. No breach of Clause 2 in this regard was ruled.

The Panel noted that there was no evidence that the Shire employee was solely responsible for the error. Nor did it consider that Shire's conduct was such as to bring discredit upon or reduce confidence in the pharmaceutical industry as alleged. No breach of Clause 2 was ruled.

Upon appeal by Genzyme the Appeal Board noted Genzyme's submission that the incorrect bar chart in Mehta *et al* had shown rates of decline of renal function in different populations of Fabry patients as measured by a fall in estimated glomerular filtration rate (GFR). The Fabrazyme data (56 men and 2 women) showed the rate of decline to be approximately 2.8ml/min/year/1.73m<sup>2</sup> which was similar to the value in males on Replagal. The actual rate of decline of estimated GFR for Fabrazyme was approximately 1.1ml/min/year/1.73m<sup>2</sup> which was close to the rate of decline in estimated GFR observed in the normal population (approximately 0.8ml/min/year/1.73m<sup>2</sup>).

The Appeal Board noted that Shire knew about the incorrect bar chart due to inter-company dialogue with Genzyme in 2009. Indeed in February 2010 Shire had given an inter-company undertaking to Genzyme that it would not deliberately refer to or use the bar chart in its uncorrected form but it reserved the right to use Mehta *et al* when accompanied by a correction notice.

The Appeal Board noted that the material from The Lancet distributed by Shire consisted of Mehta *et al* and the later corrected bar chart combined into one document. Although Shire had cited The Lancet references for Mehta *et al* and for the corrected bar chart on the front of the folder, it was not stated on the front of the folder that the second citation was a correction to the first. The front page of the reprint cited the reference Mehta *et al* but not for the corrected bar chart. Further, although the Mehta *et al* reprint included The Lancet citation as a footer to each page, the relevant citation did not appear as a footer on the one page 'Department of Error' ie the corrected bar chart. The incorrect bar chart in the Mehta *et al* reprint, did not refer to any error within and nor did it refer readers to the corrected bar chart which appeared five pages later on its own after a page of references ie after many readers might have thought that they had come to the end of the paper. In the Appeal Board's view not all readers would realise that the bar chart in Mehta *et al* was incorrect. Even if readers did find the corrected bar chart, it was not stated how it differed from the one published in the paper.

The Appeal Board considered that Shire had knowingly used promotional material which gave an

incorrect and misleading comparison of Fabrazyme with Replagal. Breaches of the Code were ruled. The Appeal Board considered that the impression given by the incorrect bar chart could not be substantiated. A breach of the Code was ruled. The appeal on these points was successful.

The Appeal Board noted that the error in the bar chart was in Shire's favour as it implied that, in terms of slowing the decline of renal function in Fabry patients, Replagal and Fabrazyme were similar. This was not so as the correct bar chart showed advantages for Fabrazyme (Genzyme's product) in this regard. In the Appeal Board's view this was a serious error and one which had been brought to Shire's attention some time ago. The Appeal Board considered that Shire's continued use of the material without ensuring readers were aware of the error was such as to bring discredit upon, and reduce confidence in, the industry. The Appeal Board ruled a breach of Clause 2. The appeal on this point was successful.

Genzyme Therapeutics Ltd complained about the use of a reprint from The Lancet (Mehta *et al* 2009) by Shire Pharmaceuticals Limited to promote Replagal (agalsidase alfa). Mehta *et al* had analysed 5-year treatment with Replagal in patients with Fabry's disease who were enrolled in the Fabry Outcome Survey observational database.

Replagal and Genzyme's product Fabrazyme (agalsidase beta) were both indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry's disease.

## COMPLAINT

Genzyme understood that Shire had made a voluntary admission on this matter as a result of recent, incomplete and failed inter-company dialogue. After learning of Shire's decision to make a voluntary admission, Genzyme made several requests to Shire for further information on the content. This was a complex case which had lasted over a number of years. Despite these requests Genzyme was unaware of the content of the voluntary admission and in particular which breaches had been admitted. Genzyme was particularly concerned that the voluntary admission might not include an adequate description of the breach in 2012 of Shire's previous written undertaking given to Genzyme in 2010. The description of this breach should include the background of Shire's intimate role in the production of the underlying misleading information and Shire's deliberate, or entirely negligent, approval of the information as promotional material in the full knowledge of the false and misleading comparison with Fabrazyme. Genzyme alleged these actions were contrary to the spirit of self-regulation and in their totality, likely to bring discredit on the industry.

Genzyme therefore complained about the breach of Shire's previous undertaking, with such serious consequences contrary to all principles of self-regulation as to bring discredit on the industry in breach of Clause 2. It also alleged breaches of Clauses 7.2, 7.3, 7.4 and de facto 1.8.

Genzyme explained that in February 2010 Shire gave an undertaking not to deliberately refer to or use an unsubstantiated, misleading and incorrectly favourable bar chart which compared Replagal with Fabrazyme and appeared in Mehta *et al.* The bar chart was subsequently corrected in 'Department of Error' (Lancet 2010).

In December 2012 Genzyme discovered that Shire had reproduced the uncorrected bar chart in a promotional piece and, after raising this issue, Shire subsequently assured Genzyme that the material (ref UK/HG/REP/12/0008a) had been recalled and to some extent repeated its previous written undertaking. The breach of Shire's original undertaking appeared to have been either deliberate or negligent both of which were unacceptably serious in terms of professional and/or procedural failings. Genzyme alleged that the breach of undertaking brought discredit to, and reduced confidence in, the industry in breach of Clause 2.

Genzyme considered the withdrawal of the incorrect and misleading promotional article following its complaint to Shire was an insufficient remedy because it had already requested that Shire stop using the incorrect material and Shire had already given a (qualified) undertaking to this effect (see below). Furthermore the misleading information was in the public domain. Genzyme therefore entered into dialogue with Shire about the distribution of a letter to explain and correct the misleading nature of the promotional piece. Shire appeared willing in this negotiation as shown in an email dated 8 March 2013 and it suggested text for a letter which Genzyme revised and returned. However Shire abruptly and unilaterally broke off dialogue stating that it would make a 'voluntary admission' which Genzyme did not consider to be truly voluntary. Furthermore Genzyme had been given no indication or assurance of the completeness of the admission, which was another reason why it had decided to complain.

Genzyme submitted that the background to the incorrect (and later corrected) Lancet publication was relevant and undisputed. Genzyme stated that in 2009 Mehta *et al.* was published in The Lancet. A bar chart in the paper depicted rates of decline of renal function in different populations of Fabry patients; this was quantified as decline of estimated glomerular filtration rate (eGFR) in millilitres/minute/year/body surface area (ml/min/year/1.73m<sup>2</sup>). The bar chart included stratified populations from the study reported, but also included references to populations from other studies. This appeared to have been done to provide comparison and context and included data for Fabrazyme, from an entirely separate study. It was concluded that this was done for the purpose of showing that the two products were largely equivalent in respect of efficacy.

The bar chart, however, contained a serious error in relation to the Fabrazyme data and depicted the rate of decline to be about 2.8ml/min/year/1.73m<sup>2</sup> which was similar to the rates shown in males for Replagal. The actual rate of decline of eGFR for Fabrazyme in the cited publication was about 1.1ml/min/year/1.73m<sup>2</sup>, which was considerably better than both the incorrect rate shown in the original bar chart and the rates prominently displayed for Replagal.

The bar chart, therefore, showed an incorrectly favourable comparison between the products. This, of course, was therefore not only unfavourable to Fabrazyme, but also, clearly misleading and unsubstantiated.

Genzyme noted that Mehta *et al.* contained a paragraph entitled 'contributors' on page 10 with the following text: ['A named author] participated in database design, data analysis and interpretation, writing, creation of figures, and study design'. In this paragraph, no other author was credited with 'creation of figures'. 'The health professional' was a former Shire employee and thus this demonstrated the clear provenance of the original error underlying the bar chart.

Discussion between Genzyme and the lead author resulted in publication of a correction in The Lancet Department of Error 2010. This correction displayed the correct rates of decline of eGFR during treatment with the two products and clearly favoured Fabrazyme.

Consistent with Lancet policy, the original publication remained unaltered on The Lancet website meaning that the correction and the original publication were quite separate in the database although there was an electronic link for researchers who used it. Whilst not ideal, Genzyme had to accept this because it was the policy of The Lancet.

However, Genzyme was particularly concerned that the error in the creation of the bar chart came directly and solely from a Shire employee and Genzyme remained unsure of exactly how the very critical error arose. The presence of the error which disparaged the efficacy of Fabrazyme was clearly very important given that the two companies were direct competitors.

Genzyme started correspondence with Shire in December 2009 immediately after The Lancet publication to point out the need for Shire to exercise appropriate professional care in directing any interested parties (internal or external) to the article or using it in promotion. During this correspondence Genzyme's fears were exacerbated when it discovered a press release from Shire drawing attention to the original article without any mention of the correction.

Shire concluded its final letter of 8 February 2010 with the following:

'As previously stated we confirm that Shire will not deliberately refer to, or use [the bar chart] in its uncorrected form.

- However Shire and all of its affiliates ("Shire") reserve the right to use,
- the Article when accompanied by the correction notice;
  - any data including the corrected [bar chart], and any other figures or tables from the Article, for any purpose(s) that Shire may deem to be appropriate in the future.'

Whilst the undertaking from Shire was not 'unconditional', Genzyme concluded that since the company was fully alerted to the error and in

accordance with the provisions of the Code, it would proscribe any use of the uncorrected bar chart in promotion or any other communication.

Genzyme was therefore dismayed and very concerned when it discovered that Shire had distributed a promotional piece (ref UK/HG/REP/12/0008a) from its stand at the Association of Inherited Cardiac Conditions, London, 19 November 2012. The promotional piece was one of a series collectively entitled 'The Replagal Reprint Collection' and was individually titled 'Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data'; the date of preparation was August 2012. The piece included a reprint of Mehta *et al* with the added published, corrected bar chart. However, the correction was entirely remote from the original incorrect bar chart. The uncorrected bar chart appeared in the main body of the text whereas the correction appeared in isolation, alone on the last page even after the references. There was no reference to it from either the incorrect bar chart or elsewhere in the body of the text and, in Genzyme's view it was unlikely that a reader would notice the presence of the correction. Even if they did, they would need to study both it and the original carefully to understand its significance in terms of the comparison with Fabrazyme.

Genzyme alleged that the use of this reprint with the uncorrected bar chart constituted a comparison with Fabrazyme which was inaccurate and based on incorrect statistics in breach of Clause 7.2, misleading in breach of Clause 7.3 and not capable of substantiation in breach of Clause 7.4. It was also in breach of Clause 1.8. Further, Genzyme alleged that Shire's use of this reprint without a clear reference to the corrected bar chart was in breach of its undertaking to Genzyme and in breach of Clause 2.

Genzyme and Shire discussed the matter and Genzyme wrote to Shire on 17 December 2012. Shire briefly replied on 3 January 2013 and stated that it had 'asked that the Sales Force no longer distribute these two articles in their current form and that any remaining copies be returned to the office for recycling'. Shire trusted that this would address Genzyme's concerns.

Genzyme interpreted Shire's letter and withdrawal of the pieces as an agreement that the material was in breach of the Code, but did not find the brief note a satisfactory remedy to the willful dissemination of knowingly misleading comparative information about Fabrazyme. It therefore wrote to Shire on 11 January and expressed continuing concerns and requested 'an unequivocal confirmation that there will be no further repeat'.

Genzyme did not receive a prompt response and sent two reminders of the need for a response which resulted (after five weeks) in Shire's letter of 15 February. Genzyme remained justifiably concerned that Shire had repeatedly failed from 2009 to adequately acknowledge and address its legitimate concerns about the use of the incorrect bar chart which was originally constructed by a Shire employee.

Genzyme therefore engaged in further dialogue with Shire in order to find a way to remedy the effect of the apparently deliberate dissemination of misleading comparative information. It appeared with the application of considerable pressure and taking into account the five week delay in response from Shire, to be arriving at a solution which would have been acceptable to Genzyme as described in the relevant emails, when Shire unilaterally broke off communication and informed Genzyme that it would make a voluntary admission, but without specifying the content despite Genzyme's requests.

Genzyme stated that this failure to self-regulate and recognize the importance of both the Code and inter-company dialogue was so serious as to risk damaging the reputation and credibility of the industry and therefore Genzyme alleged that this episode in its entirety represented a clear breach of Clause 2.

Genzyme therefore alleged that Shire had breached Clauses 1.8, 2, 7.2, 7.3 and 7.4 but stated that if Shire had already made a voluntary admission of any of these breaches it did not wish the respective complaint to be considered further.

## RESPONSE

Shire rejected Genzyme's accusations.

In December 2009, The Lancet published the results of a Fabry Outcome Survey in relation to a cohort of Fabry disease patients who had been treated for 5 years with Replagal (Mehta *et al*). The data was collated by Shire statisticians and provided to the ten authors, one of whom was a health professional then employed by Shire. Mehta *et al*, which was written by the authors with writing support from an external agency (paid for by Shire) was reviewed internally by Shire, by its authors, vetted by The Lancet and approved for publication.

Unfortunately a bar chart contained an error which was not identified in the review process. One bar purported to show the results for Fabrazyme ('for reference and comparison') and incorrectly showed the mean annualised change in GFR at -2.8ml/min/1.73m<sup>2</sup>.

When Genzyme identified and highlighted this error to Shire in December 2009, the lead author of Mehta *et al* notified The Lancet and a correction was published in January 2010. The correction was printed according to The Lancet's usual procedure for dealing with errors and a corrected bar chart was published. Shire then obtained 220 official reprints of Mehta *et al* which contained on its final page the corrected bar chart under the heading 'Department Of Error'.

On 8 February 2010 Shire confirmed the following with Genzyme:

'As previously stated we confirm that Shire will not deliberately refer to, or use [the bar chart] in its uncorrected form.

However Shire and all of its affiliates (“Shire”) reserve the right to use,

- the Article when accompanied by the correction notice;
- any data including the corrected [bar chart], and any other figures or tables from the Article, for any purpose(s) that Shire may deem to be appropriate in the future.’

Shire’s product specialists subsequently distributed the official and corrected reprints of Mehta *et al* in reprint carriers to health professionals who specialised in Fabry disease and inherited metabolic diseases. (Shire did not reproduce the uncorrected bar chart in a promotional piece. The piece referenced UK/HG/REP/0008a was the reprint carrier). The reprint carrier contained a four-page summary and an official Lancet reprint of Mehta *et al*. The reprints included the original version of the bar chart as well as the corrected version as per The Lancet’s standard practice.

Shire submitted that it had neither breached the Code nor the undertaking given to Genzyme on 8 February 2010 in circulating to physicians the official Lancet reprint of the corrected version of Mehta *et al* (which included the corrected bar chart on its last page). Shire appreciated that in not explicitly drawing attention to the corrected bar chart on the final page of the reprint, it was possible that a reader might not have noticed it. However, Mehta *et al* was only provided to physicians in its corrected (and Lancet-sanctioned) form.

It might be argued by Genzyme that Shire could have done more to highlight the correction however, Shire submitted that, in the circumstances, the steps taken to avoid misleading readers were sufficient. The official Lancet reprint showed the corrected bar chart under the heading ‘Department Of Error’ which showed it clearly to be a corrected table. Recipients of the reprint would have seen the bar chart on the back page of the reprint (its size alone made its presence obvious) and along with the heading ‘Department Of Error’ would have concluded that the back page featured the correct version of the bar chart. Indeed, as the Panel had already ruled in Case AUTH/2590/3/13, there was no breach of the Code in relation to this circulation.

Furthermore, the cover of the reprint carrier directed readers to The Lancet’s website for ‘WebExtra’ content. Here, readers would also have found a link from Mehta *et al* to the corrected bar chart. The reprint carrier and the summary of Mehta *et al* contained within it, both also contained references for the original and corrected versions of Mehta *et al*. All of the forgoing factors would have made it clear to readers that the bar chart contained within the reprint was superseded by the corrected version on the last page.

In summary, Shire submitted that it had not breached Clauses 1.8, 2, 7.2, 7.3 or 7.4. Except for the reference to Fabrazyme in the bar chart, Mehta *et al* did not discuss the relative performances of Replagal and Fabrazyme; no comparison between the two products was mentioned either in the official Lancet reprint or the summary contained in the

reprint carrier. In its undertaking of 8 February 2010 to Genzyme, Shire expressly reserved the right to use the corrected version of Mehta *et al*.

Given the period over which the parties had corresponded on this matter and the unreasonable attitude of Genzyme in attempting to ‘resolve’ it, Shire made the following comments on Genzyme’s complaint:

In the spirit of abiding by the Code and the PMCPA’s guidelines (which Shire took seriously and strove to achieve) it sought to address Genzyme’s concerns at first through inter-company dialogue.

As soon as Genzyme indicated that it was unhappy with the use of the official reprints, Shire arranged for the remaining supplies to be withdrawn from the product specialists and returned to head office as soon as practicable. The withdrawal of the reprints was not an admission of a breach of the Code. Shire’s actions were, in part, to foster goodwill between the companies given the nature of the on-going matters at the time and withdrawal was an appropriate and sufficient response in the circumstances.

Genzyme was not satisfied with the recall, and in the spirit of co-operation Shire asked Genzyme what additional action it thought was necessary. Shire then agreed to prepare a letter to be sent to recipients of the reprint and relevant stakeholders highlighting the error in the original version of Mehta *et al* and the corrected version. A copy was provided.

Shire submitted that draft for comment to Genzyme. Genzyme responded by demanding that Shire send a letter which amounted to an ‘admission’ by Shire not only of a breach of the Code (which it strongly refuted) but that Shire had deliberately provided an incorrect bar chart in order to mislead the public and discredit Fabrazyme (suggestions which Shire denied in the strongest terms). A copy of the version of the letter which Genzyme required Shire to send was provided. The situation in which Genzyme would have Shire place itself was clearly untenable and unreasonable. It was on that basis – of unreasonable and irrational demands by Genzyme – that Shire made its voluntary admission in order to resolve the matter, the response to which Shire had now received (Case AUTH/2590/3/13). Genzyme’s correspondence, demands and attitude showed that it was using the PMCPA’s procedures to wage a commercial battle and show a flagrant contempt for the self-regulatory process that it professed to support.

Genzyme’s complaint appeared to suggest that the health professional Shire employed who had contributed to Mehta *et al* (and/or Shire) had purposely submitted the incorrect data for the bar chart in order to mislead The Lancet’s readership and misrepresent Fabrazyme; this was unacceptable and untrue. In relation to the named health professional, such a suggestion by Genzyme might well amount to libel.

Genzyme's complaint (and the draft letter to health professionals it would have Shire circulate), which suggested that Shire or its employee would deliberately seek to cause The Lancet to publish false data was wrong. Such acts would not only have been unethical and exposed Shire to ridicule and censure but would likely have adversely affected the reputations of The Lancet and lead author, a renowned opinion leader. Genzyme's response was both absurd and offensive to all parties mentioned.

Genzyme referred to a press release which Shire had prepared to coincide with the publication of the original version of Mehta *et al* and the omission in that press release of any reference to the correct bar chart published by The Lancet. The draft press release referred to by Genzyme (and obtained by Genzyme in Croatia) was prepared and circulated before the error in the original version of Mehta *et al* was brought to Shire's attention. For that reason, the press release contained no acknowledgment of the error or its subsequent correction.

### **PANEL RULING**

The Panel considered that the circumstances were unusual in that during inter-company debate between Genzyme and Shire, Shire had made a voluntary admission to the PMCPA (Case AUTH/2590/3/13). Shire had not provided Genzyme with the details of its voluntary admission and the case report was yet to be published. Genzyme had not provided copies of Appendices 3-7 to its complaint. These being the press release and the email correspondence. However, the complaint to be considered was about the reprint folder used at a meeting on 19 November 2012. The folder (UK/HG/REP/12/008a) contained a four page summary (UK/HG/REP/12/008a) and the official Mehta *et al* reprint from The Lancet which included the corrected bar chart on the last page and was the same material as that which was the subject of the voluntary admission in Case AUTH/2590/3/13.

The case preparation manager had referred the case to the Panel for consideration. The Panel's role was solely to consider the case. Firstly, the Panel noted its ruling in Case AUTH/2590/3/13.

### **PANEL RULING IN CASE AUTH/2590/3/13**

The Panel noted the error in the bar chart. It also noted that Mehta *et al* did not compare Fabrazyme and Replagal in the text of their paper and once notified of the error, the lead author asked The Lancet to publish a corrected bar chart which it did. The official reprint of Mehta *et al* included the corrected bar chart on the last page; to see the corrected bar chart the reader would have to turn over the final page of the paper although the Panel noted that it was clear from the last page of the paper that something was printed on the reverse. The cover of the reprint referred the reader to The Lancet's website for WebExtra content. Once on The Lancet website, there was a link from Mehta *et al* to the corrected bar chart.

The Panel noted that Shire had distributed Mehta *et al* in a reprint folder together with a four page, A4

summary (both documents ref UK/HG/REP/12/0008a). The reprint folder front page cited both the references for the original paper and the corrected bar chart as did the front page of the A4 summary. The A4 summary gave a brief overview of Mehta *et al* and made no comparisons with Fabrazyme; neither the original nor the corrected bar chart was included in the A4 summary.

The Panel considered that it was unfortunate that Mehta *et al* had published an incorrect bar chart. Nonetheless, the reprint distributed by Shire had included the corrected bar chart, readers were directed to The Lancet website where there was a link to the corrected bar chart and the cover of the reprint carrier cited the reference for both the original paper and the corrected bar chart. Other than in the bar chart, the authors did not compare Replagal with Fabrazyme and the A4 summary of Mehta *et al* drew no comparisons between the two medicines. Taking all the circumstances into account the Panel did not consider that the material at issue was misleading. No breach of Clause 7.2 was ruled. The Panel did not consider that there had been a failure to uphold high standards. No breach of Clause 9.1 was ruled. Given these rulings, the Panel also ruled no breach of Clause 2.

### **Case AUTH/2593/4/13**

The Panel noted Genzyme's statement that if Shire had already made a voluntary admission of any of its alleged breaches of Clauses 1.8, 2, 7.2, 7.3, and 7.4 Genzyme did not want the respective complaint to be considered further.

The Panel understood the difficulties of Genzyme's position but in its view it had to consider all of Genzyme's allegations as otherwise there would be no mechanism for Genzyme to appeal any rulings of no breach of the Code (there would be no appeal of no breach rulings in a voluntary admission). In addition Paragraph 5.2 of the Constitution and Procedure stated that if a complaint concerned a matter closely similar to one which had been the subject of a previous adjudication, it may be allowed to proceed at the discretion of the Director if new evidence was adduced by the complainant or if the passage of time or a change in circumstances raised doubt 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 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 to the Appeal Board.

The Panel noted Genzyme's allegation that the use of the reprint with the uncorrected bar chart constituted an inaccurate, misleading comparison based on incorrect statistics which was not capable of substantiation. The Panel considered that the reasons for its rulings of no breach of Clause 7.2 in Case AUTH/2590/3/13 applied to the case now before it. The Panel did not consider that the material as a whole constituted a misleading comparison or was not capable of substantiation. The company had used the official Lancet reprint and had not referred to the Fabrazyme data in the A4 summary or the

reprint carrier. The Panel considered that taking all the circumstances into account the material at issue was not in breach of the Code as alleged. Thus the Panel ruled no breach of Clauses 7.2, 7.3, and 7.4.

The Panel noted Genzyme's allegations about the involvement of one of the authors who was a former Shire employee. Mehta *et al* stated under a heading 'contributors' that Shire's former employee participated in database design, data analysis and interpretation, writing, creation of figures and study design. The Panel did not know what 'participated' meant in this regard noting that Shire's former employee was the only author with 'creation of figures' listed. Genzyme alleged that the statement demonstrated the clear provenance of the original error although elsewhere in the complaint the company remained '... unsure exactly how the very critical error arose'. The Panel noted that the error in the bar chart had not been picked up in the review process which according to Shire included review by the authors, Shire and The Lancet. Shire submitted that it did not know of the error when Mehta *et al* was first published.

The Panel noted Shire had agreed with Genzyme a number of actions. Shire had also reserved the right to make certain use of the article and its correction. The outcome of inter-company dialogue was a matter for companies. The fact that a company might have not honoured its inter-company commitments was not necessarily a breach of the Code. Such a commitment was not the same as a formal undertaking given to the PMCPA by a company ruled in breach of the Code. The Panel noted its rulings above of no breach of the Code. It did not consider that Shire's use of the reprint, without a clear reference to the corrected bar chart, alleged to be in breach of Shire's agreement with Genzyme, amounted to a breach of Clause 2 as alleged. No breach of Clause 2 in this regard was ruled.

The Panel noted that there was no evidence that the Shire employee was solely responsible for the error. Nor did it consider that Shire's conduct was such as to bring discredit upon or reduce confidence in the pharmaceutical industry as alleged. No breach of Clause 2 was ruled.

Given its rulings above the Panel also ruled no breach of Clause 1.8.

## **APPEAL BY GENZYME**

Genzyme stated that the object of the appeal was to clarify the original meaning and intent of its complaint and seek four separate rulings by the Appeal Board overruling the Panel's findings that the unsolicited distribution of the Lancet reprint as promotional material did not breach Clauses 7.2, 7.3, 7.4 and 2.

Genzyme addressed these in turn below, but since it believed that its original complaint might not have sufficiently clarified this complicated case, it made the following relevant observations:

Genzyme referred to Clause 10 as an overarching provision and noted that the supplementary

information to that clause, Provision of Reprints, stated 'The provision of an unsolicited reprint of an article about a medicine constitutes promotion of that medicine and all relevant requirements of the Code must therefore be observed.'

Genzyme stated that this clause and, therefore, the Code, directly applied to this unusual and confusing case which involved the Lancet reprint which included the correction to the bar chart and which was offered as an unsolicited reprint as promotional material. In order to comply with the Code the presentation of the bar chart and its correction as promotional material required a great degree of care over and above the Lancet's policy for the correction of errors since the bar chart depicted a direct comparison between Replagal and Fabrazyme and their relative effect in preventing deterioration of renal function.

The bar chart incorrectly depicted the rate of decline of renal function during treatment with Fabrazyme as being similar to Replagal. In fact, in the source reference for the bar chart the rate of decline during treatment with Fabrazyme was approximately three times slower than was depicted. This rate of decline was also three times slower than during treatment with Replagal which indicated a substantially better treatment effect of Fabrazyme. The comparison indicating similarity in the bar chart was therefore incorrect and misleading. Furthermore it could not be substantiated since the rate of decline on Fabrazyme was incorrectly taken from the source reference. This was critically important since, as noted above, progressive renal failure was the major cause of mortality in Fabry disease.

In considering this case Genzyme stated that it did not sufficiently clarify to the Panel that, in accordance with Clause 10, the unsolicited distribution of the Lancet reprint rendered it a piece of promotional material as opposed to simply being a reprint of a Lancet article. Whilst Genzyme accepted that the reprints which Shire used for promotional purposes contained the corrected bar chart at the end of the article, Genzyme considered that the care which must be taken under the provisions of the Code when claims and comparisons were made in promotional material were more onerous in this case than simply accepting the publication policy of the Lancet which was not a promotional publication.

Genzyme noted that contrary to the conclusion of the Panel, the text of the Lancet reprint also made misleading comparisons between Fabrazyme and Replagal (in breach of Clauses 7.2 and 7.3 of the Code) and claims that were not capable of substantiation (in breach of Clause 7.4). Genzyme further noted that an employee of Shire played a significant role in the creation of the bar chart and its error. This meant that Shire had a greater obligation to ensure that the error was not propagated. Genzyme noted that it did not claim that this employee was solely responsible for the error or that it was a deliberate error.

Genzyme submitted that a three-fold greater slowing of the rate of decline of renal function (and onset of renal failure) by one product compared with the other was likely to be clinically significant in

the context of Fabry disease, as indicated both in Mehta *et al* and Waldek *et al* (2010). Mehta *et al* misrepresented the situation both graphically in the bar chart and, consequent to the erroneous graphical presentation, by omission of mention of the difference in the text which stated 'the rate of decrease in male patients was roughly two to three times greater than normal' during treatment with enzyme replacement therapy with no differentiation between the two products.

Genzyme added that inter-company dialogue and the giving of undertakings in an attempt to remedy grievances underpinned self-regulation. Any undertaking should not be given lightly and when such an undertaking was breached, this was a serious matter which undermined self-regulation and had the potential to discredit the industry.

Genzyme stated that its lack of clarity might have led the Panel to misinterpret the situation. The possible misinterpretations were illustrated by the following quotations from the Panel's ruling.

**1 'The reprint folder front page cited both the references for the original paper and the corrected bar chart as did the front page of the A4 summary.'**

Genzyme noted that in fact the simple reference 'Lancet 2010;375:200' did not indicate a 'Correction to Figure 4' [the bar chart] or a 'Department of Error' publication and could be easily construed and overlooked as a reference to correspondence, quite apart from being entirely remote from the bar chart itself. Indeed, in its ruling, the Panel discussed at length its opinion that the correction (albeit remote from the original bar chart and without any signing to it) legitimised the use of the reprint for promotional purposes. The Panel's discussion was not consistent with the clear general advice in the supplementary information to Clause 7 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'.

**2 'The Panel noted that there was no evidence that the Shire employee was solely responsible for the error.'**

Genzyme considered that in the Panel finding that there was no evidence that the Shire employee was solely responsible, it recapitulated aspects of the following text which was reproduced in full from The Lancet reprint, with the pertinent sentence highlighted:

[A named individual] participated in database design, data collection, analysis, and discussion, drafted the report, and coordinated revision by coauthors. [A named individual] obtained data and participated in the literature search and data analysis and interpretation. [A named individual] was involved in data analysis, interpretation, and writing of the report. [A named individual] was involved in data interpretation and writing of the report. [A named individual] revised the manuscript, requested and obtained additional data, and modified data analysis. [A former Shire

employee] participated in database design, data analysis and interpretation, writing, creation of figures, and study design. [A named individual] participated in study design and data collection and interpretation. [A named individual] participated in data collection and interpretation and revision of the manuscript. [A named individual] participated in database and analysis design, data collection, and revision of the manuscript. [A named individual] participated in data collection and interpretation and revision of the manuscript (emphasis added).'

In interpreting this, Genzyme alleged that it was possible, although not indicated in any way, that other authors might have been involved in the 'creation of figures', in that, while their respective individual activities were listed in detail, it was not explicitly stated that they were not involved in 'creation of figures'. Whilst it might be correct to caution that the above text did not categorically prove that a former Shire employee was solely responsible for the 'creation of figures', it was incorrect to say that there was no evidence of this. The Shire employee had a relatively prominent role of in the generation of the original error seemed beyond question, which along with Shire's sponsorship of the study indicated the need for great care in any use of the bar chart as misleading promotional material in accordance with the company's undertaking given in 2010.

**3 'Other than in the bar chart, the authors did not compare Replagal with Fabrazyme ...';**

Genzyme respectfully stated that this was not correct. Genzyme discussed text comparisons between Replagal and Fabrazyme further below under the alleged breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

**4 'The fact that a company might have not honoured its inter-company agreement was not necessarily a breach of the Code'.**

Genzyme discussed this further below under the alleged breach of Clause 2.

Genzyme stated that in view of the above considerations, the Panel's rulings, in respect of Clauses 7.2, 7.3, 7.4 and 2, were appealed as follows:

Breaches of Clauses 7.2, 7.3 and 7.4 applied under the umbrella of Clause 10

Genzyme alleged that there was no doubt that the bar chart in this piece of promotional material (as defined by Clause 10) contained a misleading, inaccurate comparison of Replagal with Fabrazyme. While a corrected version of that comparison was available on the last page of the reprint and also indirectly signed through a remote website link, supplementary information to Clause 7 stated 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc. In general **claims should not be qualified by the use of footnotes and the like'** (emphasis added). The very remote corrections of the misleading comparison, without any explanation

or interpretation, were therefore clearly inadequate as defined by the Code for use as promotional material and the unqualified presence of this incorrect and misleading comparison, which could not be substantiated was therefore in breach of Clauses 7.2, 7.3 and 7.4.

Genzyme submitted that the Panel had allowed itself to be misled by the fact that the Lancet reprint contained the corrected bar chart at the back of the article in accordance with its editorial style. Whilst this might suffice for corrections to an academic journal, it did not meet the standards set by the Code for promotional material. The fact that this was an original Lancet reprint made no difference to the need for this promotional piece to comply with the Code. The correct interpretation of the Code was made quite clear in the example given in the supplementary information to Clause 10, Quotations, 'For example, to quote from a paper which stated that a certain medicine was "safe and effective" would not be acceptable even if it was an accurate reflection of the meaning of the author of the paper, as it is prohibited under Clause 7.9 to state without qualification in promotional material that a medicine is safe'. The provisions of the Code applied equally to the use of the Lancet reprint, regardless of its authorship and the appearance of an incorrect, misleading comparison could not be justified by the remote correction, in the same way that it could not be justified by 'footnotes and the like'.

Genzyme submitted that graphical images usually had more impact than numbers in text or tables. In support of its emphasis on the bar chart rather than the text, Genzyme noted that Clause 7.8 stated 'All artwork including illustrations, graphs and tables must conform to the letter and spirit of the Code...' and from Joan Barnard's book 'Is comparison of data justified?' The Code in Practice 5th Edition, 2011. (J. Barnard Publishing) 'Bear in mind a picture speaks much louder than words and it is always the overall impression of a prominent bar chart, no matter how much text is included as qualification; a footnote will certainly not be adequate'. However, in an ideal situation, which this could not be, it would be scientifically preferable for the text to be properly corrected as well.

However, even if the Appeal Board was minded to accept the argument that the remote correction to the bar chart was sufficient to render the promotional use of the Lancet reprint (which contained the incorrect bar chart) not in breach of the Code, the text of the Lancet reprint was also in breach of Clauses 7.2, 7.3 and 7.4 and did not contain any corrections (remote or otherwise).

Genzyme respectfully noted the Panel's statement that 'Other than in the bar chart, the authors did not compare Replagal with Fabrazyme ...' was not correct. The authors stated 'Overall, the reduction of estimated GFR in female patients given enzyme replacement therapy was similar to the normal rate expected with age, whereas the rate of decrease in male patients was roughly two to three times greater than normal expected rates'. The authors referred collectively to the effect of agalsidase alfa and agalsidase beta in this sentence by using the

generic term 'enzyme replacement therapy' and indicated that the effect of the two products was the same, whereas, by contrast, elsewhere Replagal was referred to alone, and repeatedly, by its generic name 'agalsidase alfa'. Genzyme alleged that the implication that the two products were similar was clear and entirely incorrect in describing the corrected bar chart. This incorrect statement was 'misleading' in breach of Clause 7.3. It was also not 'accurate', not 'based on an up to date evaluation of all the evidence' and did not 'reflect that evidence clearly', all in breach of Clause 7.2. Finally it was not 'capable of substantiation' in breach of Clause 7.4.

Genzyme alleged that was clearly described in correspondence about the overall article in one of two letters in response to the study, which were published in The Lancet, although not referenced by Shire. Genzyme alleged that indeed this strengthened the argument that the Lancet's editorial policy on corrections might be acceptable for an academic journal where there was the possibility of such academic debate through the letters of readers and further articles but it was not acceptable for promotional material. A letter by Waldek *et al* stated: 'With the publication of the erratum for Figure 4 [the bar chart] (Jan 16, p 200), the comparison between the mean yearly fall of estimated GFR with agalsidase alfa and agalsidase beta is more accurately depicted. As reported by Germain and colleagues, the mean yearly fall of estimated GFR was  $-1.12 \text{ mL/min/1.73 m}^2$  per year for 56 men and two women receiving agalsidase beta (1 mg/kg every other week). This rate is identical to the treatment goal of  $-1.0 \text{ mL/min/1.73 m}^2$  per year as shown in the corrected Figure 4, and substantially better than the results reported by Mehta and colleagues for men treated with agalsidase alfa'.

The second letter by Deegan (2010) simply raised grave concerns about the study being a 'responder analysis' with the inherent biases. Despite these shortcomings in respect of the whole Lancet article Genzyme considered that pictures had much larger immediate impact than words and so it had concentrated on the bar chart, although it had now addressed the text as the Panel raised the issue and this appeared to have greatly influenced the Panel's conclusion that The Lancet reprint did not breach Clauses 7.2, 7.3 and 7.4.

Genzyme alleged that further if the authors had known of the error in the bar chart and the actual three fold difference between the products in the comparison chosen by the authors, they might have properly commented on it. As it was, the reprint contained inaccurate information in the text (in breach of Clause 7.2) because of its lack of comment on the three fold difference between the products as well as the text implying that the products were similar. Because the effect of the corrected bar chart was not explored in the text (indeed the text still reflected the uncorrected bar chart) this meant that even though there was a correction to the bar chart on the back page of the reprint, the use of the reprint as promotional material was in breach of Clause 7.2 because it was contradictory and therefore did not 'reflect [the] ... up-to date evaluation of all the evidence...clearly'.

## Breach of Clause 2

Genzyme alleged that in making assertions including those about libel and ridicule, Shire raised spurious distractions in order to divert attention from the point that this was a serious error involving poor quality science. The scientific error was compounded by poor promotional practice (in breach of the Code) when it was used in promotional material. It was disappointing that the error was not picked up either during review by the authors, who were experts in ultra-rare diseases or by Lancet reviewers, who might be forgiven for being less familiar with the details of treatment of these very rare diseases. However, the error, for which both Shire and its employee had significant responsibility, rendered the bar chart simply incorrect and, from a promotional point of view presented a misleading comparison to Fabrazyme which was particularly favourable to Replagal (as noted independently in Lancet correspondence).

Genzyme stated that its objective, contrary to Shire's assertions, was neither libel nor ridicule, but simply to make the point that in view of Shire's role in the provenance of the error and its previous written undertaking, it had special responsibilities in using this erroneous bar chart. Shire had failed to discharge those responsibilities and this had been manifested in its review process which allowed this reprint to be converted into inadequately corrected promotional material. It was the failure of the review process in such special circumstances and the accompanying breach of the written undertaking which was of such serious concern.

Genzyme noted that self-regulation underpinned the operation of the Code, of which inter-company dialogue, as required by the Constitution and Procedure was essential. The Panel's ruling that a written undertaking need not be honoured and the consequent precedent would render inter-company dialogue valueless and seriously threaten the basic fabric of self-regulation.

Genzyme noted that the Panel noted that 'Shire had also reserved the right to make certain use of the article and its correction'. Irrespective of any alleged 'reserved rights' Shire had an overarching obligation in using the bar chart to comply with the Code as well as the undertaking. For example it might be permissible for Shire's Medical Information Department to provide the Lancet reprint and the correction in response to an unsolicited request, although clear signing of the correction would still be required. However, as clearly laid out, Shire had breached Clauses 7.2, 7.3 and 7.4 and had therefore breached its written undertaking when properly interpreted within the framework of the Code.

Genzyme alleged that the breach of a written undertaking to another company, in rendering self-regulation worthless, risked bringing discredit to and reducing confidence in the industry and therefore constituted a breach of Clause 2. Indeed the supplementary information to Clause 2 stated 'Examples of activities which are likely to be in breach of Clause 2 include ... inadequate action leading to a breach of undertaking ...'. The

Panel asserted that a breach of an inter-company undertaking was not necessarily a breach of the Code. However the supplementary information to Clause 2 did not differentiate between undertakings given to other companies and undertakings given to the PMCPA. In Genzyme's view this was correct, for self-regulation to work, all companies which agreed to adhere to the Code must be able to have a degree of confidence in the formal undertakings of each other otherwise confidence in the industry would be reduced.

Genzyme further alleged that the use of misleading text and an incorrect and misleading bar chart which was not capable of standing alone as regards accuracy (Clause 7, supplementary information) for promotional purposes even after Genzyme had raised its concerns with Shire constituted a flagrant disregard for the accuracy of the data and therefore brought discredit to, and reduced confidence in, the pharmaceutical industry.

Finally, Genzyme noted that Shire had recently been ruled in breach of Clause 2 for similar misleading use of incorrect science for promotional purposes. The fact that this behavior had happened more than once within a short period of time made this breach even more serious and meant that there was an even greater risk that Shire's activities would bring discredit to, and reduce confidence in, the industry, in breach of Clause 2. Indeed the supplementary information to Clause 2 cited 'Examples of activities that are likely to be in breach of Clause 2... cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time'.

Genzyme requested that the Appeal Board rule that the Lancet reprint should not be used for promotional purposes without correction to the text so that the text did not continue to erroneously suggest that Fabrazyme and Replagal were equivalent in their effect and to ensure that the Lancet reprint complied with the Code.

## COMMENTS FROM SHIRE

### A Introduction

Shire submitted that in April 2013, Genzyme complained to the PMCPA about its use of the reprint from The Lancet and noted the following: Mehta *et al* contained the results of a Fabry Outcome Study in relation to a cohort of Fabry disease patients who had been treated for 5 years with Replagal. Genzyme's product, Fabrazyme, was also approved for the treatment of Fabry disease. Mehta *et al* contained an error in the bar chart relating to Fabrazyme which was subsequently corrected by The Lancet's Department of Error.

Shire submitted that Genzyme had tried to obfuscate the clear and discrete issues in play, as evidenced by four specific tactics in its appeal:

- 1 Genzyme based its allegation of breach of Clause 2 on an alleged breach of an inter-company undertaking and did not attempt to demonstrate that the terms of the undertaking were broken.

Shire contended strongly that the undertaking was not broken.

- 2 Genzyme stated that this was a complicated case and that the Panel did not understand all of the issues. This was not only unfair to the Panel but also disingenuous since the issue was clear ie was the distribution to health professionals of the official Lancet reprint with the corrected bar chart misleading under the Code?
- 3 Genzyme had sought to introduce a new issue into the appeal by questioning wording in Mehta *et al* which had not been the subject of inter-company dialogue, the inter-company undertaking or Genzyme's original complaint.
- 4 Genzyme made opportunistic use of the unrelated ruling against Shire in Case AUTH/2528/8/12.

Shire noted that in an attempt to receive guidance from the Panel it made a voluntary admission on the same matter in March 2013 (Case AUTH/2590/3/13) in which the Panel also ruled no breach of the Code. Further details were below.

Taking into account the above, Shire submitted that: the new issue should not be the subject of this appeal it had not breached its inter-company undertaking it was entitled to distribute the official, corrected reprint and the Panel's ruling of no breach of Clauses 2, 7.2, 7.3 or 7.4 should be upheld.

Shire summarised the relevant facts which culminated in the Panel's ruling of no breach in Case AUTH/2593/4/13 or Case AUTH/2590/3/13.

## **B Summary of the facts**

- 1 Genzyme complained to the PMCPA and alleged that Shire had breached an inter-company undertaking concerning the reprint of Mehta *et al* and in turn breached Clauses 2, 7.2, 7.3, 7.4 and 1.8 of the Code (the latter of which was not relevant to this appeal).
- 2 Mehta *et al* contained a bar chart which showed a decrease in renal function in patients with Fabry disease during their 5 years of treatment with Replagal. One section of the bar chart purported to show the results for Fabrazyme, for reference and comparison, but the Fabrazyme bar showed an incorrect mean.

Shire noted that Fabry disease was a rare genetic disorder resulting from the deficiency of the lysosomal enzyme  $\alpha$ -galactosidase. Renal failure, cardiomyopathy and cerebrovascular disease were the main causes of morbidity and premature death.

- 3 When this error was brought to Shire's attention by Genzyme, in December 2009, Shire immediately notified the lead author who in turn notified The Lancet and a correction was published soon afterwards. The correction was printed according to The Lancet's usual correction procedure, which meant that the material was reprinted and the correct bar chart reproduced on the reverse of the last page under the large, bold heading 'Department of Error' (which showed it clearly to be a corrected error) and the following

wording 'In this Article [...], the value shown by the third bar (in grey) in [the bar chart] was incorrect. The corrected figure is shown below.' (the 'Corrected Lancet Reprint').

Genzyme's original complaint and inter-company dialogue made much of Shire's employee's involvement but there had been a change of position on appeal. The health professional had been a Shire employee during the period of writing but had left Shire by the time of publication. This was disclosed in the corrected (and original) Lancet reprint. Genzyme had now confirmed that it was not claiming that the error was deliberate or that Shire's employee acted in any way unethically. Mehta *et al* was internally reviewed by Shire to ensure the accuracy of the Shire Fabry Outcome Survey data but Shire was not part of The Lancet's independent scientific peer review of the article.

- 4 In February 2010, Shire gave an inter-company undertaking to Genzyme that it would not deliberately refer to, or use the bar chart in its uncorrected form – which it had not done - but reserved the right to use the material when accompanied by the correction notice. Genzyme accepted this undertaking.
- 5 Copies of the corrected Lancet reprint were subsequently distributed in a folder to health professionals, specialising in the relevant field, as part of a series of articles relevant to Fabry Disease. Each folder contained a four page, A4 summary and the corrected Lancet reprint – together, the 'reprint folder' which was certified in accordance with the Code. As acknowledged by the Panel in Case AUTH/2590/3/13 (see below for details of this case), the summary contained neither the original nor the corrected bar chart. Indeed the reprint folder focussed on the conclusions drawn by the authors from the Fabry Outcome Study data.
- 6 The Panel noted in Case AUTH/2590/3/13 that readers of the reprint folder were referred to The Lancet website where there was a link from Mehta *et al* to the corrected bar chart. The Panel further noted that the cover of the reprint folder as well as the front page of the summary cited both the references for the original article and the corrected bar chart.
- 7 Shire was not in breach of its inter-company undertaking as it did not use the material in its uncorrected form and in any event, it did not follow that a breach of an inter-company undertaking resulted in a breach of the Code (this was discussed further below).
- 8 Nevertheless, when Genzyme expressed its concern, in December 2012, at the distribution of the corrected Lancet reprint (as part of the reprint folder) to health professionals, Shire withdrew the remaining folders from circulation whilst it investigated the concern. Despite confirming in the internal Shire investigation that the use of the corrected Lancet reprint meant that there had been no breach of the inter-company

undertaking, as a gesture of goodwill to facilitate the difficult ongoing relationship between the parties, Shire confirmed that it would not use the reprint folder.

- 9 The withdrawal of the reprint folder was not sufficient for Genzyme and therefore Shire agreed that it would write to the health professionals who might have received the reprint folder to highlight the error in the original version of Mehta *et al* and it provided a draft letter. The dialogue between the parties subsequently broke down when Genzyme demanded that the letter amount to an 'admission' that Shire was in breach of the Code and that it had deliberately provided an incorrect bar chart in order to mislead the public and discredit Fabrazyme, both of which Shire strongly refuted.
- 10 Consequently, Shire was placed in an unreasonable and untenable position which led to it making a voluntary admission in order to resolve the matter, for which the Panel ruled no breach of the Code (Case AUTH/2590/3/13). The Panel also found in Shire's favour in the present case (Case AUTH/2593/14/13).

### **C Preliminary issue – new Genzyme complaint on text of corrected Lancet reprint**

Shire submitted that Genzyme's appeal extended the parameters of its complaint beyond the bar chart to the text of the corrected reprint. Genzyme should not be allowed to revisit the wording of the text on appeal either because its original complaint did not succeed or it had failed to notice this issue before or omitted to raise it as an issue with Shire or the PMCPA.

Genzyme suggested that the text of the corrected reprint contained a misleading comparison between Fabrazyme and Replagal, possibly resulting from the incorrect bar chart in the original Mehta *et al*.

Genzyme alleged that as there was only two enzyme replacement therapies, Fabrazyme and Replagal, the reference to therapeutic effect without distinguishing between the two available therapies was an implied comparison.

The issue on the text of the corrected Lancet reprint had not previously been debated between the parties during the inter-company dialogue in 2009/10 about the incorrect bar chart. Neither was it raised during the inter-company dialogue about the alleged breach of undertaking in December 12 or in the March 2013 Genzyme amendments to the Shire letter to health professionals notifying them of the error in the bar chart.

In any event, Shire did not believe that by simply mentioning enzyme replacement therapies, the authors had implied any comparison between the two products but had simply tried to explain the significance of the difference between treatment and no treatment. Use of the words 'overall' and 'roughly' made in the text underlined this last point that no specific claim was made for either product.

Shire submitted that this concern could have been remedied in the same way as the incorrect bar chart. It was within the spirit of the Code for parties to attempt to resolve inter-company differences before bringing the matter to the PMCPA. Paragraph 5.3 of the Constitution and Procedure stated:

'A complaint from a pharmaceutical company will be accepted only if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter, but this offer was refused or dialogue proved unsuccessful.'

Shire submitted that therefore this appeal was not the appropriate forum for an entirely new complaint by Genzyme which the parties had not previously debated and which could have been resolved by inter-company dialogue. Genzyme had tried to introduce a new complaint through the back door which reinforced the fact that Genzyme's actions in pursuing Shire in relation to the corrected Lancet reprint were disproportionate, unnecessary and bordering on vexatious. Shire remained willing to discuss the concerns on the text of the corrected Lancet reprint with Genzyme but noted that the reprint folder had been withdrawn and was no longer in use. The Appeal Board should not consider the aspects of the appeal that related to the new complaint on the text as these were not properly the subject of this appeal.

### **D Overview of Shire's response to Genzyme's appeal**

Shire noted that Genzyme referred to the inter-company undertaking. The wording was set out directly below:

'As previously stated we confirm that Shire will not deliberately refer to, or use [the bar chart] in its uncorrected form.

However Shire and all of its affiliates ("Shire") reserve the right to use,

- the Article when accompanied by the correction notice;
- any data including the corrected [bar chart], and any other figures or tables from the Article, for any purpose(s) that Shire may deem to be appropriate in the future.'

Shire submitted that Genzyme claimed that this undertaking had been breached but did not state how. Shire had fully complied with the undertaking. It had provided Mehta *et al* in its corrected form. In accepting the undertaking, Genzyme accepted that the article could be used in this way.

Shire submitted that, putting the issue of the undertaking to one side, Genzyme's appeal appeared to advance the proposition that Shire had taken below the standard of care required for promotional material by the Code when it distributed the corrected Lancet reprint to health professionals.

In addition to the fact that the corrected Lancet reprint distributed to health professionals contained the correct bar chart, Shire strongly refuted this allegation for the following reasons: The message conveyed by the reprint folder was unconnected to the bar chart. Its focus was the conclusions drawn by the authors from the Fabry Outcome Study data and this was underlined by the fact that the summary of the corrected Lancet reprint contained neither the original nor the corrected bar chart; readers of the reprint folder were referred to The Lancet website where there was a link from Mehta *et al* to the corrected bar chart; and the front cover of the reprint folder as well as the front page of the summary cited both the references for the original article and the corrected bar chart.

Shire went above and beyond what was necessary to comply with the Code - in order to try to foster goodwill between itself and Genzyme; it withdrew the corrected Lancet reprint from circulation and offered to write to Fabry health professionals pointing out the error to address Genzyme's concerns.

Shire submitted that the original Mehta *et al* paper contained an unfortunate and genuine error which was subsequently corrected in accordance with the Lancet's standard practices. Shire had done nothing other than distribute the official corrected article (as part of a reprint folder) as it already existed in the public domain and it was highly likely that health professionals to whom the reprint folder was distributed would have already read Mehta *et al* when it first appeared in The Lancet.

Shire submitted that the essence of Genzyme's complaint was its dissatisfaction with the way in which the article was corrected. However, as the appropriate forum to raise that dissatisfaction was with The Lancet itself, Genzyme suggested that Shire fell below the standard of care required for promotional material by the Code in distributing the corrected Lancet reprint to health professionals and without taking additional steps to draw readers' attention to the corrected bar chart. However, if Genzyme's position was that the corrected reprint should never be used, that would be unsatisfactory for Shire and could have serious repercussions across the industry. The article had been reviewed by an independent expert committee at The Lancet and approved for publication. The focus of the reprint folder was the Fabry Outcome Study data and therefore the distribution of the corrected reprint in this context involved the legitimate scientific exchange of information which enhanced the scientific debate on Fabry disease, a rare genetic disorder.

Shire further submitted that there was no reason for it to take additional steps to draw readers' attention to the corrected bar chart as the message conveyed by the reprint folder was unconnected to the bar chart. Further, Shire considered that if it had highlighted the corrected bar chart in the reprint carrier as Genzyme suggested, it would have given undue emphasis to an issue which was not the central focus of the publication.

Ultimately, Genzyme had objected to the way in which the material was distributed because it had had to accept that The Lancet's style of correction was adequate for the purposes of The Lancet (despite its dissatisfaction in this regard). But Genzyme could not have it both ways: either the error was corrected sufficiently by the corrected Lancet reprint or it was not. In this respect, no distinction should be drawn between health professionals reading the corrected Lancet reprint in a scientific journal or in documents distributed to them in a promotional context. The audience was the same and they were likely to interpret the text in the same way irrespective of the way that it was communicated to them. If Genzyme was not satisfied with The Lancet's correction policy, then it should take this forward with The Lancet directly.

## **E Detailed response to points raised**

### **Genzyme's so-called 'clarifications' regarding the Panel's ruling**

Shire reiterated that Genzyme implied that the facts of this case were particularly complex, and that the Panel did not understand all the issues. This was not only unfair to the Panel, but also misleading considering that the issues at stake were clear. In particular, Genzyme wrongly suggested that the Panel was not aware of, or did not take into account, the promotional context of the distribution. However, Genzyme's insistence that its arguments must be considered under the umbrella of Clause 10 (regarding the proactive distribution of reprints) added nothing of substance to its case. It was not disputed that the reprint folder was distributed in a promotional context and it complied with the requirements of the Code as such, but this circumstance did not render its distribution in breach of the Code.

Further, Genzyme took issue with certain statements in the Panel's ruling, in particular:

'The reprint folder front page cited both the references for the original paper and the corrected bar chart as did the front page of the A4 summary.'

Genzyme alleged that the references cited on the front pages of the reprint folder and the A4 summary gave no indication of a correction to the bar chart. Genzyme also stated that the Panel legitimized the use of the corrected Lancet reprint because of the correction and alleged that the Panel's discussion was not consistent with the supplementary information to Clause 7 that 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'.

In response, Shire repeated that the focus of the reprint folder was the Fabry Outcome Study data and not the bar chart. Therefore the references to the correct bar chart were sufficient. In addition, whilst the references on the front page of the reprint folder and the A4 summary did not expressly refer to a correction, they did not imply that there

was no correction. Thus, the references simply acknowledged the content of the reprint folder and were, in this respect, neutral. The inclusion of two references on the front pages of the reprint folder and the A4 summary clearly indicated that both references were relevant and drew the reader's attention to the correct bar chart. The existence of two references would indicate that the second was an update or a correction of the former. A reasonable reader would have looked at the content of both. Finally, the supplementary information to Clause 7 was not relevant in the circumstances of the case. The corrected Lancet reprint in its entirety was capable of standing alone as regards accuracy because the error in the bar chart was rectified on the reverse of the last page of the corrected Lancet reprint which reproduced the corrected bar chart and included the heading 'Department of Error' in large, bold writing. This could not be compared to a footnote, least of all because the correction covered almost a quarter of the page. The Panel noted in Case AUTH/2590/3/13 that it was clear from the last page that something was printed on the reverse. Further, a qualification was not the same as a correction. The value of the third bar – relating to Fabrazyme - in the original bar chart was incorrect. It was not 'qualified' by the correct bar chart but rather replaced.

'The Panel noted that there was no evidence that the Shire employee was solely responsible for the error'.

Shire stated that according to Genzyme, the paragraph in the corrected Lancet reprint which stated the role of each of the authors expressly referred to a previous employee of Shire, being involved in the 'creation of figures' and therefore was evidence that the named health professional was solely responsible for the 'creation of figures' and as such, the error in the bar chart.

Shire submitted that Genzyme's argument was unclear, particularly in light of its clear confirmation that it was not claiming that the error of the named health professional employed by Shire was deliberate and that he acted in any way unethically. It appeared that Genzyme had changed its position as regards the named health professional given the Panel's ruling as Genzyme's suggestions on his involvement featured in the original complaint, the inter-company dialogue and the amendments that Genzyme made to Shire's proposed letter to Fabry health professionals.

Shire submitted that nevertheless, ignoring any insinuation of deliberate misconduct on its employee's part, it noted that a number of authors were involved in 'data collection' which would also have been relevant for the bar chart. In any event the article was subject to intense independent scrutiny. Each of the ten authors was responsible for the accuracy and balance of the article. Once all of the authors had approved the article for publication, the article was then reviewed by the scientific review committee at The Lancet. The Lancet was a highly regarded journal which insisted on intense scrutiny. For example, the scientific review committee would engage in dialogue with authors to confirm the veracity of data presented.

As demonstrated above, Shire submitted that it distributed the reprint folder (which contained the corrected Lancet reprint) in line with the Code and its inter-company undertaking. The distribution was not misleading because the corrected Lancet reprint contained the correct bar chart.

Shire submitted that the remaining two quotations were more appropriately dealt with in the section below which took Genzyme's comments to each of the Panel's rulings as regards Clauses 7.2, 7.3, 7.4 and 2 of the Code, in turn.

#### **Genzyme's comments to Panel's ruling as regards Clauses 7.2, 7.3 and 7.4**

Shire strongly contested Genzyme's arguments with regards to Clauses 7.2, 7.3 and 7.4 of the Code. The reprint folder was accurate, balanced, fair, objective and unambiguous in accordance with Clause 7.2, it did not contain misleading comparisons, it complied with Clause 7.3 and it was capable of substantiation in accordance in Clause 7.4. The Panel agreed and noted that it '... did not consider that the material as a whole constituted a misleading comparison or was not capable of substantiation. The company had used the official Lancet reprint and had not referred to the Fabrazyme data in the A4 summary or the reprint carrier'.

Further, as explained above, interpreting these clauses under the umbrella of Clause 10 did not add anything of substance to Genzyme's complaint. Genzyme suggested that this was a case about Shire's distribution of the corrected Lancet reprint and not the corrective procedure used by The Lancet to remedy the error in Mehta *et al*. However, Shire submitted that this was a spurious distinction in an attempt to substantiate a breach of the Code. Genzyme implied that The Lancet's corrective procedure might be sufficient for The Lancet but that a higher standard of care attached to material distributed promotionally and therefore the procedure used by The Lancet to correct the error in Mehta *et al* was insufficient for the reprint folder. However, essentially, Genzyme suggested that Shire could not use the corrected Lancet reprint promotionally despite its correction.

- The effect of the correction to the bar chart

Genzyme compared the correction to the bar chart in the corrected Lancet reprint to a 'footnote and the like'. Shire submitted that the correction could not be described as a footnote because it covered a quarter of a page and the nature of the correction was clearly explained on that page. Genzyme's preference might have been for the correct bar chart to have appeared alongside the incorrect bar chart but this was not in accordance with The Lancet's correction policy. Shire merely distributed copies of the official corrected reprint, which already existed in the public domain. The presence of the correct bar chart could not substantiate Genzyme's allegation that there was an incorrect and misleading comparison within the corrected Lancet reprint. Again, if The Lancet's corrective procedure was unsatisfactory to Genzyme, it should take this forward with The Lancet directly.

Shire noted that the correction was de facto obvious because its publication resulted in letters from Waldek *et al* (published in The Lancet) and Deegan (both referred to in Genzyme's appeal) regarding the implications of the corrected figure. If the correction was as remote as Genzyme suggested, it would not have been picked up by Waldek *et al* and Deegan. In any event, this reinforced the fact that an important purpose of articles such as Mehta *et al* was to generate scientific debate. If Genzyme had a criticism in respect of the article, the appropriate forum for it to voice that criticism was to comment on the article in the same way as the authors of the letters; the PMCPA was not the appropriate forum. It had so far failed to do so in the three and a half years since publication.

Shire noted that Genzyme had asserted that graphical images could have more impact than text. Therefore, Shire submitted that the correction to the bar chart (as published in the corrected Lancet reprint and later distributed as part of the reprint folder) should be sufficient. Rather than simply describe the error in the bar chart, for example by text in a footnote, the reprint reproduced the bar chart in its corrected form. Therefore any misleading comparison that might have resulted from the incorrect the bar chart was immediately remedied by the correct bar chart.

- Genzyme's speculations regarding the article

Shire submitted that Genzyme appeared to suggest that if the authors had the correct Fabrazyme data in the bar chart at their disposal when they drafted the article, they would have commented on it. This was speculation and could not be the basis of a complaint concerning serious breaches of the Code, namely Clauses 7.2, 7.3 and 7.4. The comparison to the Fabrazyme data was merely a point of reference. It was by no means the focal point of the publication, which was why the summary in the reprint folder did not refer to it. Therefore it was entirely presumptuous and misleading for Genzyme to suggest that Mehta *et al* would have commented on the comparison between Fabrazyme and Replagal and that the lack of comment rendered Shire's distribution of the corrected reprint in breach of the Code.

- Conclusion regarding Clauses 7.2, 7.3 and 7.4

To conclude, Shire strongly contested Genzyme's arguments with regard to Clauses 7.2, 7.3 and 7.4 and submitted that:

- It was true that the bar chart in Mehta *et al* contained an unfortunate error.
- The error was corrected in a manner which was sufficient to remedy that error. This was clear from the fact that at least two letters (Waldek *et al* and Deegan) were sent in response to the correction.
- It was misleading for Genzyme to refer to the corrected bar chart, which covered a quarter of a page, as a footnote.
- Genzyme's new complaint that the text of the corrected Lancet reprint was misleading was opportunistic and could and should have been

dealt with by inter-company dialogue rather than at an appeal hearing in relation to a separate complaint.

- Genzyme suggested that there had been a breach of Clause 7 due to the lack of comment on the Fabrazyme data resulting from the incorrect bar chart. This was entirely speculative given that the focus of the article was the Fabry Outcome Study data in relation to Shire's product Replagal and not the Fabrazyme data.

#### **Response to Genzyme's comments to Panel's ruling as regards Clause 2**

Shire submitted that Genzyme's allegation that the distribution of the corrected Lancet reprint was in breach of Clause 2 was not credible and as noted above, bordered on vexatious.

Shire stated that it undertook not to distribute Mehta *et al* in its uncorrected form. It had not done so, neither had Genzyme alleged this. Shire did not understand why this should result in an alleged breach of Clause 2, particularly since the inter-company undertaking specifically contemplated Shire's continuing use of Mehta *et al* in its corrected form.

Shire stated that it did not rely on the uncorrected bar chart as a promotional tactic. It distributed the official corrected Lancet reprint (containing the correct bar chart) as part of a folder. Mehta *et al* was a scientific publication and interpreted as such by its audience. Either the error contained in the publication was corrected sufficiently by the corrected Lancet reprint or it was not. In this respect, no distinction should be drawn between health professionals reading the corrected Lancet reprint in a scientific journal or in a folder of documents distributed to them promotionally. The audience was the same and was likely to interpret the text in the same way irrespective of the manner in which it was communicated (in particular considering that the bar chart was not the focal point of the reprint folder). It was just as important that health professionals were not misled by the corrected Lancet reprint when they read it in The Lancet as it was when they read the corrected Lancet reprint in the folder of documents distributed by Shire. The way that the correction was dealt with by The Lancet should not be undermined.

Shire strongly refuted Genzyme's allegation that the distribution of the reprint folder was 'poor promotional practice'. The reprint folder was certified in accordance with the robust procedures set out in Clause 14 and there was no express suggestion by Genzyme that Shire was in breach of this clause. Shire maintained its position that it did not breach the Code. By making the voluntary admission, it wanted to ensure, for the avoidance of doubt that it had not done anything unacceptable. This was twice confirmed by the Panel (Cases AUTH/2590/3/13 and AUTH/2593/4/13).

The allegation of 'poor quality science' was equally objectionable. There was a genuine error which was corrected. The term 'poor quality science' was a serious accusation which would indicate,

for example, that the Fabry Outcome Study data could not be substantiated and that the original article should be called in to question. This did not accurately reflect the circumstances of the case. Again, if Genzyme had an issue with The Lancet's corrective procedure then it should contact The Lancet directly.

Given the seriousness of the allegations made, Shire considered that it must reiterate that there was no breach of the inter-company undertaking. Shire fully complied with the undertaking and only used Mehta *et al* in its corrected form. Accordingly, Genzyme's tactic of treating the alleged breach of undertaking as a given fact without providing any explanation as to how the undertaking was breached was highly misleading.

Genzyme's argument that the alleged breach of undertaking had the potential to bring discredit upon the industry was unfounded. Genzyme's reliance on the supplementary information to Clause 2 was unconvincing. The supplementary information to Clause 2 clearly referred to a breach of an undertaking given to the Panel. This was supported by Clause 25 which stated that when an undertaking had been given in relation to a ruling under the Code, the company concerned must ensure that it complied with that undertaking. There was no analogous requirement concerning inter-company undertakings. Therefore the Panel was right that a breach of an inter-company undertaking was not necessarily a breach of the Code. This was confirmed on the PMCPA's website:

'An undertaking, given in acceptance of a ruling of a breach of the Code, is an important document. It includes an assurance that all possible steps will be taken to avoid similar breaches of the Code in future. It is very important for the reputation of the industry that companies comply with undertakings.

It is equally important that companies comply with undertakings given during the course of inter-company dialogue. **Although such undertakings are not covered by the Code, and are thus not subject to the requirements of the Code**, breaching an inter-company undertaking may indicate that previous inter-company dialogue has ultimately been unsuccessful [...].'  
(Emphasis added).

Finally, Genzyme's suggestion that there had been numerous breaches by Shire in a short period of time was particularly unfair. The reprint issues started as early as 2010 and had been the subject of protracted discussions between the parties since. Therefore not only was it opportunistic, but inappropriate for Genzyme to rely on the timing of a recent PMCPA decision against Shire on a completely different matter to try to influence the Panel's decision in this case.

In light of the above, Shire respectfully requested that the Appeal Board uphold the Panel's rulings of no breach of Clauses 7.2, 7.3, 7.4 and 2 of the Code.

## FINAL COMMENTS FROM GENZYME

Genzyme stated that in general it found that Shire's responses did not require further comment other than in repeating the arguments which Genzyme had already made in both its complaint and appeal and it referred back to them for each of Shire's points rather than repeating them at length.

However, Genzyme requested the Appeal Board deal with the following points specifically.

Shire submitted that Genzyme had used 'four specific tactics' numbered one to four, on which it commented respectively:

### A Introduction

1 Genzyme had originally found Shire's written undertaking in 'reserving rights' in respect of use of Mehta *et al*, which it had sponsored, to lack sincerity in respect of the contained direct comparison with Fabrazyme. However, Genzyme did not consider that these asserted 'rights' over-rode Shire's obligations to comply with the Code in respect of any promotional use of the publication and comparisons with Fabrazyme. The appeal was clear as to why Shire had breached these over-riding obligations and therefore also breached the inter-company written undertaking. Shire had not properly recognised these reasons either in its original non-compliant use of the reprint as promotional material or in addressing the appeal.

Genzyme stated that Shire had a clear commercial intention in its comparative promotion to create the false impression that Replagal and Fabrazyme were equally effective based on incorrect data. Shire did not have 'rights to reserve' which over-rode its obligation to comply with the Code in making its chosen comparison. If Shire wished to use the reprint for promotional purposes it must take every necessary step to ensure that the promotion complied with the Code over and above any of The Lancet's standard operating procedures. In failing to correct the bar chart in a compliant manner Shire had breached its written undertaking.

- 2 No further comment over and above the appeal.
- 3 Shire had misunderstood Genzyme's reasons for addressing the text. Genzyme stated that it had clearly stated that it simply wished to address the incorrect impression of the Panel that the comparison between Replagal and Fabrazyme was not mentioned in the text because this incorrect conclusion shaped the Panel's decision.
- 4 This was not 'opportunism', Genzyme simply wished to correct misleading comparisons made by its competitors with its products in accordance with the Code. It would be much easier for all parties if Shire desisted from making these misleading comparisons. However, since Shire persisted, Genzyme must protect its products accordingly.

## B 'Summary of the facts' third bullet

Genzyme noted that it was true that the error was corrected in accordance with The Lancet's policy. The Lancet's correction was always unsatisfactory to Genzyme and it engaged in serious debate with The Lancet which regretfully declined to change its policy and indicated that the electronic link from the original article to the correction would suffice for a diligent researcher. However, Genzyme contended strongly that the processes of diligent research and promotion were quite different and what was good for one was not necessarily good for the other. This was stated clearly in the supplementary information to Clause 10. The issues raised by the use of a single research publication in promotion were addressed in detail by the Code, particularly in respect of claims and comparisons. Publication policies of scientific journals and publications used as promotional material were quite distinct and Shire, throughout this process, appeared to ignore this distinction.

## C Preliminary issue

Genzyme noted that as stated above and clearly set out in its appeal, it had addressed this issue because the Panel had wrongly stated that the text of the publication did not refer to the comparison. Genzyme clearly stated in its appeal that it considered that the bar chart was a more powerful communication of the incorrect and misleading data than the text which was why the bar chart was the focus of its complaint. However, in its appeal Genzyme sought to address what it considered to be the Panel's misinterpretation and clarify the facts.

## D Overview of Shire's response to Genzyme's appeal

Shire stated 'In accepting the undertaking Genzyme accepted that the article could be used in this way'. Genzyme alleged that this represented Shire's misinterpretation of the Code. The reality was that Genzyme received Shire's letter after substantial dialogue and, while it noted the lack of sincerity, it interpreted Shire's undertaking within the context of its obligation to comply with the Code.

Genzyme alleged that this statement illustrated the intentional meaning of the original wording of Shire's undertaking which was that it considered it was exempt from the Code in respect of its use of the bar chart. This was exactly Genzyme's point in making this serious complaint about Shire's role in the creation of the original bar chart, its insincere undertaking, the inadequate correction of the bar chart and Shire's various unsatisfactory tactics during inter-company dialogue.

Genzyme submitted that Shire's statement 'However, as the appropriate forum to raise that dissatisfaction is with The Lancet itself' again illustrated its failure to accept that once it chose to use Mehta *et al* as a promotional piece, then Clause 10 and the Code applied. The policies of The Lancet were not relevant to the promotional practices of a company. On the other hand, the provisions of the Code, which were entirely relevant, were ignored by Shire as was foreshadowed in its insincere undertaking.

Contrary to Shire's subsequent assertions, the provisions of the Code gave every reason why Shire required extreme care in correcting the misleading comparison between its and Genzyme's product created by its own employee. Whether this poor quality science was just poor quality or otherwise was immaterial to Shire's duty of care when it made comparisons with competitors as clearly defined at length in the Code.

## E 'Detailed response to points raised.'

### 1 'Genzyme's so-called "clarifications" regarding the Panel ruling'.

Genzyme stated that it had set this out clearly in its appeal and had little to add. However, Genzyme noted that it was unable to find any previous cases about reprints, whether successful or unsuccessful. Genzyme thus concluded; that companies normally had no difficulty in determining which reprints they might or might not use in promotional material and that it was worth noting the extent and intent of Clause 10, which was entirely pertinent to this case as made clear in Genzyme's appeal.

### 2 For the reasons carefully set out above, Genzyme rejected all Shire's attempts at justifications of its promotional material and the role of its employee which led to the original erroneous and misleading comparative bar chart.

### 3 Genzyme agreed that there were potential difficulties in determining which part of the Code had been breached by Shire's purposeful activities in disseminating this incorrect and misleading comparison of the two products. In addressing this difficulty Genzyme considered that there were two vital fundamental principles of the Code. The first was that great care was mandatory when substantiating comparisons between products. The second was that honorable inter-company dialogue was pivotal. In both respects, Shire had let itself down and its words indicated that this had been purposeful. For these reasons, among the others previously stated, Genzyme alleged that the Code had been breached and the only specific and suitable clause was Clause 2.

Genzyme alleged that Shire had tried to cause distraction by stating that the term 'poor quality science' was objectionable. Alternatively Genzyme was prepared to agree that 'wrong', 'bad' or 'mistaken' could be used to describe entirely incorrect and misleading referencing of data for a comparison of therapeutic effect. However Genzyme continued to consider that 'poor quality' was a good diplomatic compromise.

Finally, Genzyme disagreed with Shire's assertion that the essence of the complaint was Genzyme's dissatisfaction with the way in which the article was corrected. Genzyme was dissatisfied with the way the article was corrected and it addressed that with The Lancet at the time. However, Genzyme had complained because Shire had used a publication for promotional purposes which did not meet the

requirements of the Code. The supplementary information to Clause 7.2 was very clear that information should be capable of standing alone and Genzyme considered that this was particularly true for graphs and charts which were often looked at in isolation.

Genzyme alleged that use of Mehta *et al* as promotional material was disingenuous because Shire knew that the bar chart was not correct as it appeared in the main article and that the correction was at the end (on the back page). Shire should have issued a notice at the front of the document to draw readers' attention to the correction (i) because the use was for promotional purposes; (ii) because one of Shire's employees had some involvement in creating the error. Shire's assertion that 'a reasonable reader would have looked at the content of both' (when discussing the references on the front page to both the corrected and the uncorrected bar chart) shifted the responsibility away from Shire to the reader. This was not in keeping with the spirit of the Code or with Clauses 7.2, 7.3 or 7.4.

### APPEAL BOARD RULING

The Appeal Board noted that Shire had distributed Mehta *et al* in a reprint folder together with a four page, A4 summary (both documents ref UK/HG/REP/12/0008a).

The Appeal Board noted Genzyme's submission that the incorrect bar chart in Mehta *et al* had shown rates of decline of renal function in different populations of Fabry patients as measured by a fall in estimated glomerular filtration rate (GFR). The Fabrazyme data (56 men and 2 women) showed the rate of decline to be approximately 2.8ml/min/year/1.73m<sup>2</sup> which was similar to the value in males on Replagal. The actual rate of decline of estimated GFR for Fabrazyme was approximately 1.1ml/min/year/1.73m<sup>2</sup> which was close to the rate of decline in estimated GFR observed in the normal population (approximately 0.8ml/min/year/1.73m<sup>2</sup>).

The Appeal Board noted that Shire knew about the incorrect bar chart due to inter-company dialogue with Genzyme in 2009. Indeed in February 2010 Shire had given an inter-company undertaking to Genzyme that it would not deliberately refer to or use the bar chart in its uncorrected form but it reserved the right to use Mehta *et al* when accompanied by a correction notice.

The Appeal Board noted that The Lancet had its own policies and procedures for correcting published articles within its journal and on its website. However, as Shire had used the reprint including the corrected bar chart to promote Replagal it had to ensure that the material complied with the Code.

The Appeal Board noted that the material from The Lancet distributed by Shire consisted of Mehta *et al* and the later corrected bar chart combined into one document. Although Shire had cited The Lancet references for Mehta *et al* (Lancet 2009; 374: 1986-96) and for the corrected bar chart (Lancet 2010; 375: 200) on the front of the folder, it was not stated on the front of the folder that the second citation was a correction to the first. The front page of the reprint gave the reference Lancet 2009; 374: 1986-96 but did not include the reference Lancet 2010; 375: 200. Further, although the Mehta *et al* reprint included The Lancet citation as a footer to each page, the relevant citation did not appear as a footer on the one page 'Department of Error' ie the corrected bar chart. The incorrect bar chart in the Mehta *et al* reprint, did not refer to any error within and nor did it refer readers to the corrected bar chart which appeared five pages later on its own after a page of references ie after many readers might have thought that they had come to the end of the paper. In the Appeal Board's view not all readers would realise that the bar chart in Mehta *et al* was incorrect. Even if readers did find the corrected bar chart, it was not stated how it differed from the one published in the paper.

The Appeal Board considered that Shire had knowingly used material to promote Replagal which included a bar chart which gave an incorrect and misleading comparison of Fabrazyme with Replagal. Breaches of Clauses 7.2 and 7.3 were ruled. The Appeal Board considered that the impression given by the incorrect bar chart could not be substantiated. A breach of Clause 7.4 was ruled. The appeal on these points was successful.

The Appeal Board noted that the error in the bar chart was in Shire's favour as it implied that, in terms of slowing the decline of renal function in Fabry patients, Replagal and Fabrazyme were similar. This was not so as the correct bar chart showed advantages for Fabrazyme (Genzyme's product) in this regard. In the Appeal Board's view this was a serious error and one which had been brought to Shire's attention some time ago. The Appeal Board considered that Shire's continued use of the material without ensuring readers were aware of the error was such as to bring discredit upon, and reduce confidence in, the industry. The Appeal Board ruled a breach of Clause 2. The appeal on this point was successful.

**Complaint received**

**10 April 2013**

**Case completed**

**7 August 2013**