

CODE OF PRACTICE REVIEW

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

PUBLIC REPRIMAND FOR ALLERGAN

Allergan Limited has been publicly reprimanded by the Code of Practice Appeal Board for successively failing to comply with an undertaking originally given in Case AUTH/2183/11/08 by continuing to claim that Vistabel/Botox was clinically more potent than Bocouture/Xeomin (Case AUTH/2460/11/11 and Cases AUTH/2487/3/12 and AUTH/2489/3/12).

In 2011, and again in 2012, the Code of Practice Panel ruled breaches of the Code in relation to the activities of Allergan's field-based staff (Case AUTH/2460/11/11) and its placement of advertisements (Cases AUTH/2487/3/12 and AUTH/2489/3/12) which misrepresented data relating to the relative potencies of Allergan's medicines (Vistabel/Botox) vs Merz's medicines (Bocouture/Xeomin).

In Case AUTH/2460/11/11, the Panel noted that Allergan had previously been ruled in breach of its original undertaking and so given the repeated serious breach of the Code, it reported Allergan to the Appeal Board. On consideration of that report (February 2012), the Appeal Board was concerned that Allergan's comments upon it and presentation to the Appeal Board revealed a marked lack of insight and objectivity. An undertaking was an important document and Allergan's successive breach of it was unacceptable. The Appeal Board required an audit of Allergan's procedures in relation to the Code (April 2012) and subsequent re-audits.

In Cases AUTH/2487/3/12 and AUTH/2489/3/12, the Panel again reported Allergan to the Appeal Board for another breach of its original undertaking in Case AUTH/2183/11/08. On consideration of that report (June 2012), the Appeal Board noted that Allergan's fourth breach of its undertaking was completely unacceptable. The Appeal Board required an audit of Allergan's procedures in relation to the Code to be carried out concurrently with those required in Case AUTH/2460/11/11.

On consideration of the first audit report (April 2012), the Appeal Board did not consider that Allergan's procedures were satisfactory; it was disappointed at the lack of progress demonstrated at the second audit in August 2012. After a third audit in January 2013, the Appeal Board noted that progress had been made but further improvement was necessary. The company was audited again in September 2013 whereupon the Appeal Board noted that more progress had been made and on the basis that Allergan implemented its compliance plans, the Appeal Board decided that no further action was required.

Full details of Case AUTH/2460/11/11 can be found on page 3 of this issue of the Review; full details of Cases AUTH/2487/3/12 and AUTH/2489/3/12 are on page 14.

activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of newly introduced requirements.

There are different transitional provisions for certain clauses. Details are given in the supplementary information to those clauses.

PRICE REDUCTIONS

As companies are aware, the revised Statutory Scheme, the alternative to the Pharmaceutical Price Regulation Scheme requires list prices of medicines to be reduced by 15% with effect from 1 January 2014.

It is in the interest of advertisers to indicate the new lower prices on promotional material as soon as possible. In the period 1 January 2014 – 30 April 2014 however, promotional material will not be considered to be in breach of the Code if it still carries the previous higher price.

Care should be taken, however, to ensure that there is no discrepancy between what representatives say and what is on written material left with doctors etc by representatives as this could give rise to complaints.

It will not be acceptable at any time to give comparative prices in promotional material if these involve the new lower prices of the advertiser's products and the superseded higher prices of competitor products.

Every effort should be made to ensure that journal advertisements are correct at the time of publication.

PROVIDE ACCURATE INFORMATION

As a case unfolds, it can sometimes become apparent that a company's submission to the Authority, or to the Panel, has been inaccurate. Effective self regulation relies on full, frank and wholly accurate disclosure from the outset. To do otherwise risks compromising confidence in the industry. The provision of inaccurate or misleading information is seen as a major failing and is likely to result in the relevant company being reported to the Code of

2014 CODE

Proposals for amendment of the ABPI Code and the PMCPA Constitution and Procedure were agreed at the Half Yearly General Meeting of the ABPI on 5 November.

The changes to the Code of Practice come into operation on 1 January 2014 but, during the period 1 January to 30 April, no promotional material or

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CODE OF PRACTICE TRAINING

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

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

The next Code of Practice seminar date on which places remain available is:

Monday 3 February 2014

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

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

HOW TO CONTACT THE AUTHORITY

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

Telephone: 020 7747 8880
Facsimile: 020 7747 8881

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

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

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

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

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

2014 CODE... (Continued from cover)

The 2014 Code cross refers to requirements in the Second 2012 Edition of the Code regarding publication of certain fees for services and other payments.

Details of the changes together with a PowerPoint presentation and a copy of the 2014 Code are available on the PMCPA website. The interactive 2014 Code and other materials will be updated shortly.

PROVIDE ACCURATE INFORMATION... (Continued from cover)

Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. When it considers the report, the Appeal Board will decide whether to impose any of the sanctions listed in Paragraph 11.3.

Companies must thus ensure that *all* information provided to the Authority, or to the Panel, is accurate; attention to detail in this regard cannot be over emphasised. Companies must impress upon third parties, whether agencies or overseas parents/affiliates, that it is extremely important that any data they provide must also be wholly accurate. It is better to ask for an extension to allow for the submission of accurate information than to submit inaccurate data in the first instance and correct it later.

ABPI EXAMINATION

Accredited examinations will be offered by the ABPI from January 2014 as a new Level 3 qualification.

The new exams are the Medical Representatives Examination (Level 3 Diploma in the promotion of prescription medicines) and the Generic Sales Representatives Examination (Level 3 Certificate in the promotion of prescription medicines).

Bookings for these exams will be through a new website (<http://exams.abpi.org.uk>) which goes live in December. Anyone registering on the new website will take the accredited exams.

Candidates who are part way through the exam will be able to continue to take unaccredited exams. Candidates who are already registered, but who are yet to take any exams, will be offered the opportunity of switching to the accredited exam if they wish. Unaccredited exams will be offered until December 2015.

Please contact Sarah Jones, ABPI Head of Education and Exam (sjones@abpi.org.uk) for further details.

MERZ/DIRECTOR v ALLERGAN

Breach of undertaking

Merz alleged that at a meeting and through the conduct of one of its representatives, Allergan had continued to misrepresent data relating to the relative potencies of its medicines Vistabel/Botox (botulinum toxin type A (onabotulinumtoxinA)) vs Merz's medicines Bocouture/Xeomin (botulinum toxin type A (incobotulinumtoxinA)). As Merz alleged that Allergan had breached the undertakings given in Cases AUTH/2183/11/08 and AUTH/2346/8/10 this case was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The detailed response from Allergan is given below.

The presentation at issue was given by an Allergan scientific services manager at an aesthetic practitioners meeting. Merz alleged that claims were made about the relative potency of Vistabel vs Bocouture – a comparison which had been the subject of Case AUTH/2346/8/10 – and built the case that the units of potency of the products were not interchangeable and that Bocouture was less potent than Vistabel. The presentation specifically did not reflect the Bocouture summary of product characteristics (SPC) which stated: 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'.

Merz submitted that in Case AUTH/2346/8/10 the Appeal Board stated that 'both the Bocouture SPC and data on file that support the SPC statement were available to Allergan when the presentation [at issue in that case] was delivered but were nonetheless not included'. Allergan had again presented a discussion about product potency excluding not only the regulator's view but now also that of the Appeal Board. No new independent data to change understanding of relative potencies had been published. In fact since the Appeal Board's ruling a 1:1 conversion ratio between Botox (Vistabel) and Xeomin (Bocouture) had been made even more clear with the publication of the Xeomin 50 unit SPC in May 2011 which stated: 'Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1'.

Merz alleged that the Allergan presentation referred to non-interchangeability of unit doses directly quoted from the product SPCs yet it again failed to mention the regulatory view of the relative potencies. Merz noted that the botulinum toxin in both Vistabel and Bocouture came from the Hall strain of clostridium botulinum and as such would not be expected to demonstrate different clinical effect.

The Allergan speaker then presented data from Moers-Carpi *et al* (2011) to further develop the impression that Bocouture was less potent than Vistabel. Merz submitted that the design of this study was open to significant question as there was no control arm and unmatched doses of each product were used.

Merz stated that prior to the publication of this recent data it had been established, and reflected in the SPCs, that the correct starting dose for Vistabel and Bocouture in the treatment of moderate to severe glabellar frown lines was 20 units. Carruthers *et al* (2005) demonstrated that Botox 20U and 30U showed no measurable clinical difference in the treatment of moderate to severe frown lines and postulated that in most patients a 20U dose was sufficient to saturate the local nerve endings so that additional dosing had little or no incremental clinical effect.

The new Allergan study compared 30U of Bocouture with 20U of Vistabel in moderate to severe frown lines. Merz alleged that the crafting of this presentation, the selective use of data, and what could only be a deliberate omission of the established regulatory position to leave the impression of reduced potency of Bocouture to Vistabel was cynical and in breach of previous undertakings made by Allergan.

The Panel noted that in Case AUTH/2346/8/10, the Appeal Board considered that a presentation by Allergan had implied that Botox was more potent than Xeomin which was inconsistent with the SPCs and clinical data. Although the material at issue in Case AUTH/2346/8/10 differed from that in Case AUTH/2183/11/08, the Appeal Board considered that the overall effect was sufficiently similar to the point at issue in Case AUTH/2183/11/08 for it to be caught by the undertaking in that case and so breaches of the Code were ruled including a breach of Clause 2.

The Panel noted that Bocouture/Xeomin contained the same active constituent as Botox/Vistabel, ie botulinum toxin type A (BONT/A). In all of the products the neurotoxin was derived from an identical strain.

The Panel noted that there appeared to be no standard assay method for the two BONT/A preparations. The SPCs for Botox/Vistabel referred to Allergan Units/vial and the Bocouture/Xeomin SPCs referred to LD50 units per vial. The Xeomin SPC stated that due to differences in the LD50 assay, these units were specific to Xeomin and were not interchangeable with other botulinum toxin preparations. All of the SPCs stated that as the botulinum toxin units differed from product to product, doses recommended for one product were not interchangeable with those for another. The

Bocouture SPC, however, stated that comparative clinical study results suggested that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900kD) [Botox/Vistabel] were of equal potency. The Xeomin 50 units SPC contained the equivalent statement but added 'when used with a dosing conversion ratio of 1:1'. In this regard the Panel noted that Sattler *et al* (2010) demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin to Botox/Vistabel in the treatment of frown lines. The SPCs for Bocouture and Vistabel stated identical recommended unit doses for the treatment of moderate to severe frown lines, ie five injections each of 4 units. The Bocouture SPC stated that the dose might be increased to up to 30 units if required by the individual needs of the patient.

The title of the presentation at issue was 'Botulinum Toxin Review and Update'. The second slide stated that the most potent of the seven botulinum neurotoxin serotypes was type A, the active constituent of Vistabel and Bocouture. It was also stated that unit doses of botulinum toxin were not interchangeable from one product to another. Slide 14 of the presentation depicted the SPCs for, *inter alia*, Bocouture and Vistabel and the heading referred to the 'non-interchangeability of units of BONT-A products'. Although the relevant statement in the Bocouture SPC was highlighted, the subsequent statement that comparative clinical study results suggested that Bocouture and Botox/Vistabel were of equal potency was not and nor was this information given in any other slide.

The final section of the presentation headed 'Introduction to Clinical Trials' discussed non-inferiority studies in general and the last 19 slides in particular detailed the results of Moers-Carpi *et al* which compared the efficacy of Vistabel (20 units) vs Bocouture (30 units) in the treatment of patients with moderate/severe glabellar lines. There was no explanation as to why different doses of the two medicines had been chosen despite the doses (in numbers of units) recommended in the respective SPCs being identical. The slide which introduced the study stated that 20 units of Vistabel and 30 units of Bocouture both represented labelled doses. It did not appear, however, that information about the doses chosen in the study had been presented within the context of the SPC recommendations, ie that the starting dose for Bocouture was 20 units which could be increased to up to 30 units if required. The slide headed 'Study Conclusions' stated that Vistabel (20 units) was as effective as Bocouture (30 units) in the treatment of glabellar lines and that the study reinforced the data previously reported by Hunt *et al* (2010). The Panel noted that there was no reference in the presentation to Sattler *et al* although the speaker submitted he/she had mentioned that the study had shown that in the same therapy area 24 units of Bocouture was non-inferior to 24 units of Vistabel.

The Panel also noted that there was no reference in the presentation to Carruthers *et al*, the dose ranging study with Botox/Vistabel which had shown that in the treatment of frown lines doses of 30 or

40 units did not produce statistically significantly better results than a dose of 20 units and that the majority of patients responded well to 20 units with some needing a higher dose to achieve the same effect. Although this was a Botox/Vistabel study, the Panel considered that it demonstrated an important point which would have helped to provide context to the rest of the presentation. The Panel noted that Allergan had provided a copy of data on file from Merz which it stated demonstrated a dose response for Bocouture/Xeomin between 10, 20 and 30 units when used to treat frown lines. When determined by the investigator at day 30, the percentage of responders to 20 units and 30 units was 74.5 and 91.7 respectively. It was not stated in the information before the Panel whether this was a statistically significant difference.

Overall, the Panel considered that the presentation did not reflect the balance of evidence with regard to the relative potencies and was concerned to note that, as acknowledged by Allergan, it had not been reviewed or approved for use at the meeting. In the Panel's view the presentation implied that Botox/Vistabel was more potent than Bocouture/Xeomin. In that regard the Panel considered that this was sufficiently similar to the point at issue in Case AUTH/2346/8/10 for it to be covered by the undertaking in that case and to breach undertakings given previously. In that regard high standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Panel ruled a breach of Clause 2.

Merz stated that an Allergan sales representative, in a visit to a customer who used Bocouture, used the Moers-Carpi *et al* poster to support the assertion that the potency of Bocouture was inferior to that of Vistabel. The poster directly referred to the Hunt and Clark data that was the subject of the breach of undertaking in Case AUTH/2346/8/10. The customer was clearly left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

The Panel noted that the Vistabel sales aid provided by Allergan as the only promotional item that referred to Moers-Carpi *et al* was entitled 'Not all toxins are Vistabel'. The front cover included with the statement 'Vistabel unit doses are not interchangeable with other preparations of botulinum toxins'. One page was headed 'Head-to-head data review of glabellar lines' beneath which were a very brief description of Sattler *et al* and a more detailed description of Moers-Carpi *et al*. Subsequent pages of the sales aid detailed the results of Moers-Carpi *et al* with the use of a bar chart and graph. The back page included the claim 'A recently conducted equivalence study confirms that unit doses of Vistabel and Merz toxin are not interchangeable in clinical practice' referenced to Moers-Carpi *et al*. There was no reference on the

back page to Sattler *et al.* There was no mention of the statement in the Bocouture SPC that clinical data suggested equal potency.

There was no complaint about the sales aid. However, the Panel considered it was relevant to the allegation that the customer was left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

The Panel noted that the Moers-Carpi *et al* poster was not available for representatives to distribute; if customers asked for a copy the representatives had to ask medical information to send a copy or receive a copy themselves in a sealed envelope for delivery. Allergan had acknowledged that three customers had asked the representative for a copy of the poster.

The Panel noted that it was impossible to know what the representative had said or whether the representative had used the sales aid. However, the Panel considered that, given the content of the sales aid, on the balance of probabilities, the representative had used the Moers-Carpi *et al* poster to inform the health professional that in order to achieve the same clinical outcome in the treatment of glabellar lines 20 units of Vistabel was needed vs 30 units of Bocouture ie unit for unit, Bocouture, was less potent than Vistabel.

The Panel noted its comments above with regard to the clinical data and the statement in the Bocouture SPC. Noting the content of the sales aid the Panel considered that the arranged provision of the Moers-Carpi *et al* poster by the representative would, on the balance of probabilities, leave the health professional with the impression that Bocouture did not possess the same clinical potency as Vistabel as alleged. In the Panel's view this breached the undertakings previously given. In that regard high standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

The Panel noted that Allergan had again breached undertakings with regard to claims about the relative potency of its botulinum toxin vs that of the Merz product. In the Panel's view, the repeated and serious nature of such breaches of the Code raised concerns about the company's procedures and warranted consideration by the Appeal Board. In accordance with Paragraph 8.2 of the Constitution and Procedure, the Panel reported the company to the Appeal Board.

The Appeal Board noted that Allergan had accepted the breaches of the Code and that it had already undertaken meaningful action to improve its culture and processes to avoid similar errors in the future. Further steps to improve compliance were planned.

The Appeal Board considered that the company's comments on the report and presentation revealed a marked lack of insight and objectivity. Given that potency comparisons between Botox and Xeomin had previously resulted in two breaches of undertaking it was vital that Allergan briefed, trained and had systems in place such that its staff did not use material that could result in a further breach of undertaking or the use of unapproved slides. The Appeal Board considered that an undertaking and assurance was an important document and it was extremely concerned that Allergan had now breached its undertaking and assurance on three separate occasions in a short space of time. This was completely unacceptable.

The Appeal Board decided that Allergan should be publicly reprimanded for successive breaches of its undertaking. The Appeal Board also decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of Allergan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in April 2012. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

On receipt of the April 2012 audit report the Appeal Board considered that Allergan's procedures were not satisfactory. The Appeal Board was extremely disappointed that there was insufficient responsibility taken across the company for Code compliance. Company culture did not appear to support compliance with the Code. The Appeal Board noted that it had already publicly reprimanded Allergan.

The Appeal Board decided that Allergan should be re-audited in three months' time at which point it expected there to be significant improvement. As part of the usual re-audit process Allergan would be asked to provide an update of its response to the first audit report with actions and timelines. Upon receipt of the report for the re-audit, the Appeal Board would decide whether further sanctions were necessary.

The Appeal Board subsequently decided in Cases AUTH/2487/3/12 and AUTH/2489/3/12 to require an audit which would be conducted at the same time as the re-audit required in this case (Case AUTH/2460/11/11).

On receipt of the August 2012 audit report the Appeal Board was disappointed at the lack of progress demonstrated. However the company appeared to have taken action including setting time frames for the bulk of the processes and work to be completed by the end of 2012. The Appeal Board was concerned that the amendments to some of the standard operating procedures (SOPs) had not been finalized. The Appeal Board noted that there were plans to significantly change the company structure and the interim country manager would be replaced in 2013. A UK medical director was due to be appointed. The Appeal Board considered that Allergan should be re-audited in January 2013 at which point it expected there to be significant improvement.

Upon receipt of the January 2013 audit report, the Appeal Board noted that although Allergan had made progress, further improvement was necessary. The Appeal Board noted that one key change in senior personnel would take place shortly and another in due course. Given that further improvement was required, the Appeal Board considered that Allergan should be re-audited in September 2013. Upon receipt of the next audit report, the Appeal Board would decide whether further sanctions were necessary.

Upon receipt of the September audit report, the Appeal Board noted that Allergan had made progress since the re-audit in January. The company had undergone four audits since April 2012. It was important that the progress shown in the September 2013 audit was continued and maintained. Every opportunity should be taken for improvement. The Appeal Board noted that Allergan needed to ensure that it updated its processes in good time to reflect the 2014 Code and that relevant staff were trained on the new Code. Allergan provided details of its plans to implement the recommendations in the audit report. On the basis that this work was completed, the Appeal Board decided that no further action was required.

Merz Pharma UK Ltd alleged that Allergan Limited had continued to misrepresent data relating to the relative potencies of its medicines Vistabel/Botox (botulinum toxin type A (onabotulinumtoxinA)) vs Merz's medicines Bocouture/Xeomin (botulinum toxin type A (incobotulinumtoxinA)). As Merz alleged that Allergan had breached the undertakings given in Cases AUTH/2183/11/08 and AUTH/2346/8/10 this case was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Merz explained that in accordance with Paragraph 5.3 of the Constitution and Procedure it had not sought to resolve this matter through inter-company dialogue with Allergan. It was apparent that despite repeated reinforcement of the importance of undertakings this consistent behaviour suggested either poor understanding of the Code coupled with systemic compliance incompetence or contempt; neither was appropriate within the industry.

By way of background Merz noted that in Case AUTH/2183/11/08 Allergan was ruled in breach of the Code for suggesting that Xeomin (the same pharmaceutical product as Bocouture) was less potent than Botox (the same pharmaceutical product as Vistabel). Following this Allergan entered into an undertaking not to use this or similar claims. This undertaking was breached twice in Cases AUTH/2335/7/10 and AUTH/2346/8/10 and Allergan entered into yet another undertaking. It was clear that Allergan had again breached the undertaking and the fact that two employees from different parts of the business had delivered the same message within a week of each other suggested this was a behaviour born out of a clear brief.

Merz was concerned that Allergan was relentless in its pursuit of the message that the Bocouture and

Xeomin units were less potent than the Vistabel and Botox units against all the clinical evidence and the view of the Medicines and Healthcare products Regulatory Agency (MHRA) and the wider European regulators. In pursuit of this message Allergan was clearly as contemptuous of the PMCPA, the Code of Practice Appeal Board and its undertakings as it was of the regulators and the peer reviewed published evidence.

By way of background, Allergan explained that it did not accept the allegations from Merz that it had made 'disparaging, misleading and unsubstantiated' claims about the relative potency of Bocouture/ Xeomin vs Vistabel/Botox or that these claims constituted a breach of undertaking. Allergan took exception to the tone and language within Merz's complaint and strongly refuted the serious and disparaging allegations made. Allergan was aware and fully understood the undertakings made with respect to Case AUTH/2183/11/08 and Case AUTH/2346/8/10 (which was ruled on along with Case AUTH/2355/7/10). It took any undertaking seriously and certainly would not treat them with contempt as erroneously suggested by Merz.

The undertakings in all three cases fundamentally related to the use of animal data (Hunt and Clarke, 2006 and 2009). More specifically, the undertaking in Case AUTH/2183/11/08 centred around the use of these animal data, which should not be extrapolated to the clinical situation unless there were data to show it was of direct relevance and significance.

Case AUTH/2346/8/10 (and Case AUTH/2335/7/10) again centred on the use of Hunt and Clarke data and the fact that it implied that Botox was more potent than Xeomin, which was inconsistent with the summaries of product characteristics (SPCs) and the recently available clinical data from Merz. The data had not been sufficiently contextualised and therefore the presentations at issue in both cases were found in breach of the ruling in Case AUTH/2183/11/08.

With respect to the current alleged breach of undertaking at two events, no animal data relating to the Hunt and Clarke study (at the centre of the original undertaking in Case AUTH/2183/11/08) nor indeed any animal potency determination data were presented. In both instances directly relevant and significant, new clinical data were presented, which Allergan believed substantially changed the scientific landscape and understanding of non-interchangeability of potency units of botulinum toxins. These data supported Allergan's assertion (as stated in the SPCs for all botulinum toxin products and throughout the presentation) that units doses were not interchangeable from one product to another.

At the heart of these issues were the two companies' understanding of the SPCs and how the information should be interpreted and presented in a balanced way to health professionals.

For clarity Allergan reproduced the various SPC statements:

The SPCs for Botox 50, 100 and 200 units stated:

‘Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan units are different from other botulinum toxin preparations’

The SPC for Vistabel stated:

‘Considering that botulinum toxin units are different depending on the medicinal products, doses of botulinum toxin are not interchangeable from one product to another.’

The SPC for Xeomin (50 units) stated:

‘Due to unit differences in the LD50 assay, Xeomin units are specific to Xeomin. Therefore unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.’

Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1.’

The SPC for Xeomin (100 units) stated:

‘Unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.’

The SPC for Bocouture stated:

‘Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.’

Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency.’

Allergan considered that the most prominent and significant statement in all of the botulinum toxin SPCs was that unit doses of products were not interchangeable. This statement of non-interchangeability was imposed on all botulinum toxin manufacturers by the Pharmacovigilance Working Party (PhVWP) which, following a class review in 2006, mandated that all botulinum toxin SPCs included wording to highlight the non-interchangeability of unit doses between products, in order to ensure the safe and appropriate use of botulinum toxins. In the two events at issue where Merz had alleged a breach of undertaking, Allergan submitted that it had clearly communicated the non-interchangeability of unit doses, supported by new clinical data, not that Merz’s toxin was less potent than Allergan’s. This was the message that Allergan had always wanted to convey. Allergan fully accepted and understood the rulings in the previous cases. However, at these two events no undertaking had been breached as no animal data had been used, despite the availability of substantial new clinical data from an appropriately powered

(n=220), randomised, double-blind, peer reviewed equivalence study. It had not been stated or implied that Merz’s products were less potent, only that they were not the same and that unit doses were not interchangeable. Allergan had been required to make this explicitly clear to customers in part because of Merz’s marketing strategy of promoting a 1:1 conversion ratio as demonstrated in a recent advertisement (a copy was provided) and indeed in Merz’s complaint itself. Allergan considered that this strategy fundamentally contradicted the intent of the PhVWP when it mandated that all botulinum toxin SPCs included wording (in bold) to highlight the non-interchangeability of unit doses between products to ensure the safe and appropriate use of botulinum toxins.

Assessment of potency was a laboratory measure, using an LD50 assay, and was not a recognised endpoint in clinical studies. Each botulinum toxin manufacturer had its own unique and proprietary potency assay methodology. Consequently, the PhVWP’s mandated statement that unit doses of the botulinum toxin containing products were not interchangeable be included in all SPCs including that of Xeomin and Bocouture. Allergan did not believe that this requirement was superseded by a contradictory statement based upon clinical studies of a non inferiority design. Non-inferiority studies could not demonstrate equivalence. Allergan noted that in Case AUTH/2270/10/09, the Appeal Board’s view was that the results of a non-inferiority study could not be used to claim equivalence. It was noted that the expression ‘suggest ... are of equal potency’ (emphasis added) had been used in the Bocouture SPC.

The suggestion by Merz of ‘a dosing conversion ratio of 1:1’ between Xeomin/Bocouture and Botox/Vistabel was of significant concern. No ‘dosing conversion’ occurred or should be implied from the non-inferiority studies conducted by Merz with its toxin.

Allergan considered that the direct medical impact was that a significant patient safety risk existed with prescribers encouraged to transfer information from one label to another product.

1 Meeting presentation

COMPLAINT

Merz alleged that in November 2011 a scientific support manager from Allergan gave a presentation on botulinum toxins at a practitioners meeting. Merz believed that the presentation was promotional and thus fell within the scope of the Code.

The presentation was prefaced with the metaphor that although all beer was made from water, malt, hops and yeast, different beer strengths could be created from the same ingredients. The presentation went on to make claims about the relative potency of Vistabel vs Bocouture – a comparison which was previously the subject of Case AUTH/2346/8/10 – and built the case that the units of potency of the products were not interchangeable and that

Bocouture was less potent than Vistabel. The presentation specifically did not include or reflect the position of the European regulator which opposed this view and was included in section 4.2 of the Bocouture SPC which stated:

‘Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency’.

Merz submitted that in Case AUTH/2346/8/10 the Appeal Board stated that ‘both the Bocouture SPC and data on file that support the SPC statement were available to Allergan when the presentation was delivered but were nonetheless not included’. Allergan had again presented a discussion about product potency excluding not only the regulator’s view but now also that of the Appeal Board. No new independent data to change the up-to-date understanding of relative potencies had been published and as such the scientific landscape remained unchanged. In fact since the Appeal Board’s ruling the regulator had made its view even more clear, specifying a 1:1 conversion ratio between Botox (Vistabel) and Xeomin (Bocouture) with the publication of the Xeomin 50 unit SPC in May 2011 which stated in section 4.2:

‘Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1.’

Merz alleged that the Allergan presentation referred to non-interchangeability of unit doses directly quoted from the product SPCs yet it again failed to mention the regulatory view of the relative potencies. Merz noted that the botulinum toxin in both Vistabel and Bocouture came from the same (Hall strain) clostridium botulinum and as such would not be expected to demonstrate different clinical effect.

The Allergan speaker then presented data from a recent non-peer reviewed poster authored by two Allergan employees together with a third author (Moers-Carpi *et al* 2011) to further develop the impression that Bocouture was less potent than Vistabel. Merz submitted that the design of this study was open to significant question as there was no control arm and unmatched doses of each product were used, making a potency comparison difficult.

Merz stated that prior to the publication of this recent data it had been established, and reflected in both product SPCs, that the correct starting dose for Vistabel and Bocouture in the treatment of moderate to severe glabellar frown lines was 20 units. This starting dose had been further investigated by Carruthers *et al* (2005) who compared 4 doses (10U, 20U, 30U and 40U) of Botox in eighty females with moderate to severe glabellar frown lines. The study demonstrated that Botox 20U and 30U showed no measurable clinical difference and the authors concluded that there ‘were no statistically significant

differences among the three higher-dose groups’. It was postulated that in most patients a 20U dose was sufficient to saturate the local nerve endings so that additional dosing had little or no incremental clinical effect.

The new Allergan study compared 30U of Bocouture with 20U of Vistabel in moderate to severe glabellar frown lines. Merz alleged that the crafting of this presentation, the selective use of data, and what could only be a deliberate omission of the very clearly established regulatory position to leave the impression of reduced potency of Bocouture to Vistabel was both cynical and clearly in breach of previous multiple undertakings made by Allergan.

RESPONSE

Allergan provided a copy of the presentation at issue with a document from the speaker, a scientific services manager, outlining his/her recollection of what was said. No materials had been provided to the delegates.

Allergan noted that the presentation did not refer to the Hunt and Clarke (2006 or 2009) data and this data was not discussed during the presentation. Slides 9-14, 19, 21 and 48 covered the topic of non-interchangeability and potency was referred to in some of these but specifically in the context of potency units being specific to each product. There was no statement, suggestion or inference that one product was less potent than another, just that each botulinum toxin was unique. The speaker provided a summary of how the ‘beer’ analogy and slide had been discussed.

Allergan noted that the presentation did not specifically include the statement in the Bocouture SPC that ‘Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency’. However, as stated in his/her summary the speaker clearly referred to Sattler *et al* (2010), the non-inferiority study upon which the SPC statement was based. The speaker would have included slides on the study itself if the presentation time had not been significantly reduced at short notice by the meeting organisers.

Allergan considered the issue of non-interchangeability was addressed appropriately prior to the introduction of significant new clinical data (Moers-Carpi *et al*).

In contradiction of Merz’s allegations, these data had been peer reviewed by the scientific committees of European Masters in Anti-Aging Medicine (EMAA) and further information from this study had also been peer reviewed and accepted for a poster presentation at the American Society for Dermatologic Surgery (ASDS).

Allergan submitted that this new peer-reviewed equivalence study (Moers-Carpi *et al*) had been published since the rulings in the cases cited above and indeed since the update to the SPC labelling

of Bocouture and Xeomin 50 units in the UK. These new data from a large (n=220) randomised, double blind, equivalence study directly challenged the hypothesis that the products were indeed interchangeable at a 1:1 dose ratio and had provoked significant interest in the scientific and clinical community, which was, at the same time, seeing contradictory weekly advertisements from Merz in the BMJ quoting a 1:1 ratio.

Allergan was surprised to note that Merz had erroneously referenced Botox dose ranging data in relation use in glabellar lines, stating that this meant the dose ranging for Bocouture would be similar. The Botox dose ranging publication (Carruthers *et al*) stated, 'It should be noted that the results reported in this study refer to the Allergan (Irvine, CA, USA) formulation of botulinum toxin type A (Botox, Botox Cosmetic, Vistabel) and cannot be generalized to other formulations or serotypes of botulinum toxin'. Furthermore, Merz had conducted its own dose-ranging clinical study of Bocouture (data from which was presented publicly at the European Academy of Dermatology and Venerology conference in 2009 and subsequently sent to Allergan in July 2010 following an information request, as it did not believe these data had been published in a peer reviewed journal). This dose-ranging study by Merz stated that there was indeed a dose response for Bocouture between 10, 20 and 30 units when used in glabellar lines (Merz - Data on File; a copy was provided by Allergan). Allergan submitted that the differences seen for Botox and Bocouture in clinical dose ranging studies further supported the non-interchangeability of potency units in a clinical setting. This was also supported by regulatory agency assessments of the products, as there were differences between the labels for Vistabel and Bocouture, where a single dose of 20 units was indicated for Vistabel as compared to 20-30 units for Bocouture.

Allergan was deeply concerned that the UK label for Bocouture contained an inaccurate, contradictory and hence misleading statement:

'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.'

Comparative clinical study results suggest that Bocouture and the comparator product containing Botulinum toxin type A complex (900kD) are of equal potency.'

Allergan had been in confidential correspondence with the PhVWP about its concerns and understood that a label change had subsequently been requested by Germany (reference member state for Xeomin and Bocouture) following discussions at the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

Allergan strongly denied that the presentation had breached an undertaking. There was no statement, suggestion or inference that one product was less potent than another, only that each botulinum toxin was unique. The animal data at issue in the previous

cases was not presented. The new clinical data presented was used to support Allergan's assertion (as stated in the SPCs for all botulinum toxin products) that units doses were not interchangeable from one product to another.

Allergan stated that the slide deck used at the meeting in November had been reviewed and it regretted to inform the PMCPA that it had not been reviewed or approved for use at the meeting. Allergan acknowledged that this was a clear breach of the Clause 14.1. The failure to seek appropriate review and approval of the presentation meant that the employee and therefore Allergan had failed to maintain high standards in breach of Clause 9.1.

The employee had been told that failure to get the presentation approved was a very serious matter, in breach of Clause 14.1 and of Allergan policy and procedures. As a consequence a full internal investigation had been instigated and would result in appropriate disciplinary action for the employee.

Allergan took this matter extremely seriously and, apart from actions being undertaken with the employee, it would reinforce the requirement for approval of all presentations with all relevant personnel. Any repeat of such failures would result in disciplinary action including dismissal of individuals responsible for such breach.

In response to a request for further information Allergan stated there was a verbal invitation for the scientific services manager to be an expert speaker at the meeting. This was followed up by an email.

The slide deck used by the manager built on a slide deck that had been approved as a core set of Medical Affairs slides. This core set could be selected from by the medical affairs team but any selection from the set required approval of the presentation prior to use in breach of Clause 14.1.

PANEL RULING

The Panel noted that in Case AUTH/2346/8/10, the Appeal Board considered that a presentation by Allergan had implied that Botox was more potent than Xeomin which was inconsistent with the product SPCs and the available clinical data. Although the material at issue in Case AUTH/2346/8/10 differed from that in Case AUTH/2183/11/08, the Appeal Board considered that the overall effect was sufficiently similar to the point at issue in Case AUTH/2183/11/08 for it to be caught by the undertaking in that case and so breaches of the Code were ruled including a breach of Clause 2.

Turning to the case now before it, Case AUTH/2460/11/11, the Panel noted that Bocouture/Xeomin contained the same active constituent as Botox/Vistabel, ie botulinum toxin type A (BONT/A). In all of the products the neurotoxin was derived from the identical Hall strain of Clostridium botulinum type A. Bocouture/Xeomin which was free from complexing proteins had a molecular weight of 150kD whilst Botox/Vistabel was associated with other proteins and had a higher

molecular weight (900kD). The SPCs for Botox/Vistabel stated that under physiological conditions it was presumed that the complex dissociated and released the pure neurotoxin.

The Panel noted that there appeared to be no standard assay method for the two BONT/A preparations. The SPCs for Botox/Vistabel referred to Allergan Units/vial and the Bocouture/Xeomin SPCs referred to LD50 units per vial. The Xeomin SPC stated that due to differences in the LD50 assay, these units were specific to Xeomin and were not interchangeable with other botulinum toxin preparations. All of the SPCs stated that as the botulinum toxin units differed from product to product, doses recommended for one product were not interchangeable with those for another. The Bocouture SPC, however, stated that comparative clinical study results suggested that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900kD) [Botox/Vistabel] were of equal potency. The Xeomin 50 units SPC contained the equivalent statement but added 'when used with a dosing conversion ratio of 1:1'. In this regard the Panel noted that Sattler *et al* (2010) demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin (n=277) to Botox/Vistabel (n=93) in the treatment of glabellar frown lines. The SPCs for Bocouture and Vistabel stated identical recommended unit doses for the treatment of moderate to severe glabellar frown lines, ie five injections each of 4 units. The Bocouture SPC stated that the dose might be increased to up to 30 units if required by the individual needs of the patient.

The Panel noted that the presentation at issue had been given at an aesthetic practitioners meeting. The title of the presentation was 'Botulinum Toxin Review and Update'. The second slide stated that the most potent of the seven botulinum neurotoxin serotypes was type A, the active constituent of Vistabel and Bocouture. It was also stated that unit doses of botulinum toxin were not interchangeable from one product to another. Slide 14 of the presentation depicted the SPCs for, *inter alia*, Bocouture and Vistabel and was headed 'Summary of product characteristics recognises the non-interchangeability of units of BONT-A products'. Although the relevant statement in the Bocouture SPC was highlighted, the subsequent statement that comparative clinical study results suggested that Bocouture and Botox/Vistabel were of equal potency was not and nor was this information given in any other slide.

The final section of the presentation headed 'Introduction to Clinical Trials' discussed non-inferiority studies in general and the last 19 slides in particular detailed the results of Moers-Carpi *et al* which compared the efficacy of Vistabel (20 units, n=105) vs Bocouture (30 units, n=104) in the treatment of patients with moderate/severe glabellar lines. There was no explanation as to why different doses of the two medicines had been chosen despite the doses (in numbers of units) recommended in the respective SPCs being identical. The slide which introduced the study stated that 20 units of Vistabel and 30 units of Bocouture both represented

labelled doses. It did not appear, however, that information about the doses chosen in the study had been presented within the context of the SPC recommendations, ie that the starting dose for Bocouture was 20 units which could be increased to up to 30 units if required. The slide headed 'Study Conclusions' (the last slide in the presentation before the Vistabel prescribing information) stated that Vistabel (20 units) was as effective as Bocouture (30 units) in the treatment of glabellar lines and that the study reinforced the data previously reported by Hunt *et al* (2010). The Panel noted that there was no reference in the presentation to Sattler *et al* although the speaker submitted in an account of the meeting that he/she had talked about the data and that the study had shown that in the same therapy area 24 units of Bocouture was non-inferior to 24 units of Vistabel. The Panel queried how much time the speaker would have had to explain the Sattler *et al* data given that he/she had otherwise presented 50 slides in 30 minutes.

The Panel also noted that there was no reference in the presentation to Carruthers *et al*, the dose ranging study with Botox/Vistabel which had shown that in the treatment of frown lines doses of 30 or 40 units did not produce statistically significantly better results than a dose of 20 units and that the majority of patients responded well to 20 units with some needing a higher dose to achieve the same effect. There were 10 patients in each treatment group. Although this was a Botox/Vistabel study, the Panel considered that it demonstrated an important point which would have helped to provide context to the rest of the presentation. The Panel noted that Allergan had provided a copy of data on file from Merz which it stated demonstrated a dose response for Bocouture/Xeomin between 10 (n= 48), 20 (n=47), and 30 (n=48) units when used to treat glabellar lines. When determined by the investigator at day 30, the percentage of responders to 20 units and 30 units was 74.5 and 91.7 respectively. It was not stated in the information before the Panel whether this was a statistically significant difference.

Overall, the Panel considered that the presentation did not reflect the balance of evidence with regard to the relative potencies of Botox/Vistabel vs Bocouture/Xeomin and was concerned to note that, as acknowledged by Allergan, it had not been reviewed or approved for use at the meeting. In the Panel's view the presentation implied that Botox/Vistabel was more potent than Bocouture/Xeomin. In that regard the Panel considered that this was sufficiently similar to the point at issue in Case AUTH/2346/8/10 for it to be covered by the undertaking in that case. Thus the presentation now at issue breached undertakings given previously. A breach of Clause 25 was ruled. In that regard high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Panel ruled a breach of Clause 2.

2 Conduct of a representative

COMPLAINT

Merz stated that an Allergan sales representative visited a customer who used Bocouture. The representative used an A4 copy of the Moers-Carpi *et al* poster to support his assertion that the potency of Bocouture was inferior to that of Vistabel. A direct copy of the poster given to the customer was provided. The poster concluded:

'This clinical study found that 20 units of onabotulinumtoxinA [Vistabel] are as effective as 30 units of incobotulinumtoxinA [Bocouture] in reducing the severity of glabellar lines 28 days post injection, and demonstrated a trend in favour of onabotulinumtoxinA at days 84, 98 and 112. These results were obtained despite a 50% higher dose of incobotulinumtoxinA than onabotulinumtoxinA.'

The poster further added 'Results reinforce reported biological activity data (1,2) ...' and directly referred to the Hunt and Clark data that was the subject of the breach of undertaking in Case AUTH/2346/8/10. The customer was clearly left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

RESPONSE

Allergan confirmed that requests from three of the representative's customers for copies of the Moers-Carpi *et al* poster had been forwarded to the medical information department. These responses were provided to the customers in line with Allergan's Medical Information and Healthcare Compliance procedures. Without knowing the identity of the doctor in question Allergan could not provide any further specific information to refute the allegations made by Merz or provide a comprehensive account of the representative's recollection of what was said. However, Allergan's records showed that its representative had responded appropriately to the three requests for copies of the Moers-Carpi *et al* poster.

Allergan confirmed that the representative had passed the ABPI Medical Representatives Examination.

Allergan denied that it had breached its undertakings in Case AUTH/2183/11/08, AUTH/2346/8/10 and AUTH/2335/7/10 and therefore denied any breach of Clauses 25, 9.1 or 2.

In response to a request for further information Allergan stated that it had one promotional item which referred to the Moers-Carpi *et al* poster. A copy was provided. The field force was not given copies of the Moers-Carpi *et al* poster or briefed to use it with customers. Any unsolicited requests for the poster were forwarded to medical information. Allergan provided part of its healthcare compliance training slide set which covered how Allergan briefed representatives to handle requests for reprints/clinical papers and posters. The Moers-Carpi *et al* poster was not on the approved list of materials which could

be requested by the field force. A copy of the list of materials/reprints which could be requested was provided. Therefore, any requests for the poster were directed to medical information.

The representative had forwarded three unsolicited requests for the Moers-Carpi *et al* poster to the medical information department. The poster was sent direct to one customer and the representative delivered it to the other two in sealed envelopes which were left unopened with the customers.

PANEL RULING

The Panel noted that the Vistabel sales aid (ref UK/0775/2011) provided by Allergan as the only promotional item that referred to Moers-Carpi *et al* was entitled 'Not all toxins are Vistabel'. The front cover included the statement 'Vistabel unit doses are not interchangeable with other preparations of botulinum toxins'. One page in the sales aid was headed 'Head-to-head data review of glabellar lines' beneath which was boxed text with a very brief description of Sattler *et al* and a more detailed description of Moers-Carpi *et al*. Subsequent pages of the sales aid detailed the results of Moers-Carpi *et al* with the use of a bar chart and graph. The back page of the material included the claim 'A recently conducted equivalence study confirms that unit doses of Vistabel and Merz toxin are not interchangeable in clinical practice' which was referenced to Moers-Carpi *et al*. There was no reference on the back page to the Sattler *et al* non-inferiority study which showed that 24 units of Bocouture/Xeomin was non-inferior to 24 units of Botox/Vistabel in the treatment of glabellar lines. There was no mention of the statement in the Bocouture SPC that clinical data suggested equal potency.

There was no complaint about the sales aid. However, the Panel considered it was relevant to the allegation that the customer was left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

The Panel noted that the Moers-Carpi *et al* poster was not available for representatives to distribute; if customers asked for a copy the representatives had to ask medical information to send a copy or receive a copy themselves in a sealed envelope for onward transmission to the customer. Allergan had acknowledged that three customers had asked the representative for a copy of the poster. In that regard the Panel noted Allergan's submission that the requests were unsolicited. In the Panel's view, the emphasis on the Moers-Carpi *et al* data within the sales aid meant that any request for a copy of the poster which was prompted by a representative's discussion of that data was a solicited request for the poster.

The Panel noted that it was impossible to know what the representative had said to any of the three customers about the poster or whether the representative had used the sales aid. However, the Panel considered that, given the content of the sales aid, on the balance of probabilities, the representative had used the Moers-Carpi *et al* poster to inform the

health professional that in order to achieve the same clinical outcome in the treatment of glabellar lines 20 units of Vistabel was needed vs 30 units of Bocouture ie unit for unit, Bocouture was less potent than Vistabel.

The Panel noted its comments in point 1 above with regard to the clinical data and the statement in the Bocouture SPC that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900kD) are of equal potency'. Noting the content of the sales aid the Panel considered that the arranged provision of the Moers-Carpi *et al* poster by the representative would, on the balance of probabilities, leave the health professional with the impression that Bocouture did not possess the same clinical potency as Vistabel as alleged. In the Panel's view this breached the undertakings previously given. A breach of Clause 25 was ruled. In that regard high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

* * * * *

The Panel noted its rulings in this case that Allergan had again breached undertakings with regard to claims about the relative potency of its botulinum toxin vs that of the Merz product. Case AUTH/2346/8/10 had also been ruled in breach of Clauses 2, 9.1 and 25. In the Panel's view, the repeated and serious nature of such breaches of the Code raised concerns about the company's procedures and warranted consideration by the Appeal Board. In accordance with Paragraph 8.2 of the Constitution and Procedure, the Panel reported the company to the Appeal Board.

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COMMENTS FROM ALLERGAN ON THE REPORT

Allergan submitted that it understood the reasoning behind the breaches ruled. It took the Panel's rulings extremely seriously and assured the Appeal Board that it was committed at a senior management level and throughout the organisation to abide by the Code. There was no deliberate decision to ignore recommendations from previous cases or any 'systemic incompetence' or 'contempt' for the Code as suggested by Merz. Allergan provided detailed comments on the case and the actions it had taken. Allergan stated that it had taken on board all the learnings from this case and would fully address these moving forward.

At the consideration of the report Allergan acknowledged that failings had occurred but submitted that it had already partially implemented a number of actions to address the issues raised in this case including: brand team process for all materials; acceleration of a competency framework for copy

reviewers; setting compliance goals and objectives; a review of all healthcare compliance training materials; increased impact of monthly Code updates; retraining of staff, a quality management system investigation and Corrective and Preventative action (CAPA) plan reviewed and monitored by the UK management team and compliance committee and finally a review and update of all relevant healthcare compliance and medical information SOPs. Allergan submitted that it would show its continued commitment through robust CAPAs.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that Allergan had accepted the breaches of the Code and that it had already undertaken meaningful action to improve its culture and processes to avoid similar errors in the future. Further steps to improve compliance were planned. The Appeal Board considered that the breaches of undertaking were a company issue not solely the responsibility of one individual.

The Appeal Board considered that the company's comments on the report and presentation revealed a marked lack of insight and objectivity. Given that potency comparisons between Botox and Xeomin had previously resulted in two breaches of undertaking it was vital that Allergan briefed, trained and had systems in place such that its staff did not use material that could result in a further breach of undertaking or unapproved slides. The Appeal Board considered that an undertaking and assurance was an important document and it was extremely concerned that Allergan had now breached its undertaking and assurance on three separate occasions in a short space of time. This was completely unacceptable.

The Appeal Board decided that Allergan should be publicly reprimanded for successive breaches of its undertaking. The Appeal Board also decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of Allergan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in April 2012. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

FURTHER APPEAL BOARD CONSIDERATION

On receipt of the April 2012 audit report the Appeal Board considered that Allergan's procedures were not satisfactory. The Appeal Board was extremely disappointed that there was insufficient responsibility taken across the company for Code compliance. Company culture did not appear to support compliance with the Code. The Appeal Board noted that it had already publicly reprimanded Allergan.

The Appeal Board decided that Allergan should be re-audited in three months' time at which point it expected there to be significant improvement. As part of the usual re-audit process Allergan would be asked to provide an update of its response to the first audit with actions and timelines. Upon receipt of the report for the re-audit, the Appeal Board would decide whether further sanctions were necessary.

The Appeal Board subsequently decided in Cases AUTH/2487/3/12 and AUTH/2489/3/12 to require an audit which would be conducted at the same time as the re-audit required in Case AUTH/2460/11/11.

Although the Appeal Board was disappointed, on receipt of the August 2012 audit report, at the lack of progress demonstrated, the company appeared to have taken action including setting time frames for the bulk of the processes and work to be completed by the end of 2012. The Appeal Board was concerned that the amendments to some of the standard operating procedures (SOPs) had not been finalized. The Appeal Board noted that there were plans to significantly change the company structure. The Appeal Board considered that Allergan should be re-audited in January 2013 at which point it expected there to be significant improvement.

Upon receipt of the January 2013 audit report, the Appeal Board noted that although Allergan had made progress, further improvement was necessary. The Appeal Board noted that one key change in senior personnel would take place shortly and another in due course. Given that further improvement was required, the Appeal Board considered that Allergan should be re-audited in September 2013. Upon receipt of the next audit report, the Appeal Board would decide whether further sanctions were necessary.

Upon receipt of the September audit report, the Appeal Board noted that Allergan had made progress since the re-audit in January. The company had undergone four audits since April 2012. It was important that the progress shown in the September 2013 audit was continued and maintained. Every opportunity should be taken for improvement. The Appeal Board noted that Allergan needed to ensure that it updated its processes in good time to reflect the 2014 Code and that relevant staff were trained on the new Code. Allergan provided details of its plans to implement the recommendations in the audit report. On the basis that this work was completed, the Appeal Board decided that no further action was required.

Complaint received	30 November 2011
Undertaking received	26 January 2012
Appeal Board Consideration	23 February, 24 May, 11 October 2012, 6 March 2013
Interim Case Report first published	17 July 2012
Case completed	15 October 2013

MERZ/DIRECTOR v ALLERGAN

Breaches of undertaking

Merz alleged that, by again making disparaging, misleading and unbalanced claims about the comparative potency/clinical efficacy of its own products Vistabel/Botox (onabotulinumtoxinA) vs that of Bocouture/Xeomin (incobotulinumtoxinA), Allergan had breached undertakings given in previous cases. Merz marketed Bocouture/Xeomin.

The matters were taken up with the Director acting as the complainant as the PMCPA was responsible for ensuring compliance with undertakings.

Merz submitted that the claims at issue were consistent with previous breaches of undertaking, most recently Case AUTH/2460/11/11 together with Cases AUTH/2183/11/08 and AUTH/2346/8/10. These cases clearly demonstrated a flagrant disregard for the Code and associated sanctions. Merz alleged that Allergan's actions in Cases AUTH/2487/3/12 and AUTH/2489/3/12 were covered by the same undertakings as in the previous cases.

In Case AUTH/2487/3/12 the material at issue was an article in *Cosmetic News*, March 2012. The article 'Dosages for botulinum toxins are not interchangeable says study' was written as if it were an Allergan press release. At issue in Case AUTH/2489/3/12 was a substantially similar article in the *International Journal of Aesthetic and Anti-Ageing Medicine (PRIME)*, a UK-based publication, March 2012, entitled 'BTX-A [botulinum toxin A] Dosing Not Interchangeable'.

The articles summarised Moers-Carpi *et al* (2011), (a poster presented at a European meeting in September 2011) that was the subject of the breach of undertaking in Case AUTH/2460/11/11. This was a non-peer reviewed poster authored by two Allergan employees and a third author. The articles made claims about the potency of Vistabel compared with Bocouture – a comparison which had been the subject of Cases AUTH/2460/11/11 and AUTH/2346/8/10 – with the intention of implying that Bocouture was less potent than Vistabel.

Merz considered that the design of Moers-Carpi *et al* was open to significant question; there was no control arm and unmatched doses of each product were used (20 units of Vistabel, 30 units of Bocouture) making potency comparison difficult. In Case AUTH/2460/11/11 the Panel concluded that the use of Moers-Carpi *et al* data alone did not reflect the balance of evidence and Merz alleged that this was also the case with the two articles in question. The data had not been used in the context of the summaries of product characteristics (SPCs) recommendations for either product of the same starting dose of 20U. Additionally the data was not contextualised, there was no reference to the regulatory approved study data (Sattler *et al* 2010) which demonstrated non-inferiority between the two medicines at a 1:1 dosing conversion ratio.

Merz noted that the articles also did not refer to Carruthers *et al* (2005) which compared Botox in eighty females with moderate to severe glabellar frown lines at the doses of 10U, 20U, 30U and 40U. The study demonstrated that Botox showed no measurable clinical difference between 20U and 30U; the authors concluded that there 'were no statistically significant differences among the three higher-dose groups'. It was postulated that in most patients 20U was sufficient to saturate the local nerve endings so that additional dosing had little or no incremental clinical effect.

In summary Merz noted that Allergan had been ruled in breach for suggesting that Xeomin (the same pharmaceutical product as Bocouture) was less potent than Botox (the same pharmaceutical product as Vistabel) in Case AUTH/2183/11/08. Following this Allergan gave an undertaking not to use this or similar claims. This undertaking was breached twice in Cases AUTH/2335/7/10 and AUTH/2346/8/10 and Allergan gave yet another undertaking. In Case AUTH/2460/11/11 Allergan was again ruled in breach of an undertaking relating to product potency claims in relation to Bocouture. Within only one month of the outcome of Case AUTH/2460/11/11, Allergan had briefed a third party to promote the same unbalanced data that it was not able to promote directly.

Merz was concerned that Allergan was relentless in its pursuit of the message that the Bocouture and Xeomin units were less potent than the Vistabel and Botox units against all the clinical evidence and the view of the Medicines and Healthcare products Regulatory Agency (MHRA) and the wider European regulators. Furthermore, Merz had been able to comment on an article in the March issue of *Cosmetic News* up until 23 February which was some time after the ruling for Case AUTH/2460/11/11.

The detailed response from Allergan is given below.

The Panel noted that Allergan had been notified of the outcome of Case AUTH/2460/11/11 on 26 January 2012, four days before it sent a press release about the Moers-Carpi *et al* (2011) data to *Cosmetic News* and *PRIME*; the subsequent articles were published in the March edition of the journals. In Case AUTH/2460/11/11, Allergan was again ruled to have breached undertakings with regard to claims about the relative potency of its botulinum toxin vs that of the Merz product. One of the matters at issue was about the emphasis given to the Moers-Carpi *et al* results in the relative absence of other data. Allergan accepted the rulings and signed the relevant undertaking on 3 February 2012; there was no reference in the undertaking to any other material already in press. The Panel noted the submission from Merz that it had been given up until 23 February to comment on an article

which was to be published in the March editions of *Cosmetic News* and *PRIME*. Allergan submitted that after it had sent the press release on 30 January, it had not had any further contact with the journals or been offered the chance to comment on the articles. The Panel noted that Allergan's PR agency had provided the press release following its contact with the editor of *Cosmetic News* and *PRIME* (30 January) in the period when Allergan, having received the notification of the Panel's rulings of breaches in Case AUTH/2460/11/11 (26 January) and report to the Code of Practice Appeal Board, would be deciding whether to accept or appeal those rulings (due 3 February). The Panel also noted that the press release was examined and signed on 25 January which was whilst Allergan was awaiting the outcome of Case AUTH/2460/11/11.

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the publisher/journalist and not on the content of the article itself. The articles at issue reproduced large sections of Allergan's press release. The press release was headed 'New study provides further evidence that dosing for botulinum toxins are not interchangeable'; the sub-heading read 'Head to head study launched at international aesthetics congress further reinforces need for awareness of the different doses for two botulinum toxin type A products'. The press release ended with a quotation from one of the authors of Moers-Carpi *et al*, an Allergan employee; 'We are pleased to see further evidence for the efficacy of Vistabel and consider that this study provides further clarity that Vistabel and the Merz unit doses are not interchangeable in clinical practice'.

The Panel noted that in Case AUTH/2460/11/11 both parties had submitted more information than above. The Panel thus noted elements of its rulings in that case.

In addition it noted that in Case AUTH/2346/8/10 Allergan had been ruled in breach of its undertaking given in Case AUTH/2183/11/08 in that an impression was given that Botox was more potent than Xeomin and this was inconsistent with the SPCs and available clinical data. Breaches of the Code including Clause 2 were ruled.

Turning to the cases now at issue, Cases AUTH/2487/3/12 and AUTH/2489/3/12, the Panel noted that the press release in question (Date of preparation Dec 2011) was itself undated. It had been examined by Allergan on 25 January 2012 according to the certificate. The press release was only about the Moers-Carpi *et al* data. The results of that study had not been set within the context of the recommended doses for Vistabel and Bocouture according to their SPCs, the statement in the Bocouture SPC that comparative clinical study results suggested that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900kD) [Botox/Vistabel] were of equal potency and the clinical results of Sattler *et al* which showed that 24 units of Bocouture/Xeomin was non-inferior to 24 units of Botox/Vistabel in the treatment of glabellar lines.

The Panel did not consider that the discussion of Moers-Carpi *et al*, in isolation, in the press release represented the balance of the evidence with regard to the relative efficacy of Vistabel and Bocouture. In the Panel's view, the press release implied that in order to achieve the same clinical outcome in the treatment of glabellar lines, 20 units of Vistabel was needed vs 30 units of Bocouture, ie unit for unit, Bocouture was less potent than Vistabel. In that regard the Panel considered that the press release was sufficiently similar to the point at issue in Cases AUTH/2346/8/10 and AUTH/2460/11/11 for it to be covered by the undertaking in Case AUTH/2346/8/10. Thus the press release now at issue breached an undertaking previously given. A breach of the Code was ruled in each case. These rulings were appealed by Allergan.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking were such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2 which was appealed by Allergan.

The Panel was concerned that Allergan stated that it had reviewed the press release in relation to the outcome of Cases AUTH/2335/7/10 and AUTH/2346/8/10 and that the press release had been sent out when Allergan would be considering whether to appeal yet another breach of undertaking ruled by the Panel in Case AUTH/2460/11/11. Given the seriousness of the situation, the Panel considered that Allergan should have taken urgent action and considered not using the press release until it had decided whether to appeal Case AUTH/2460/11/11, particularly as the form of undertaking required withdrawal of any similar material. Allergan could have contacted the editor of both journals following its provision of the undertaking in Case AUTH/2460/11/11. However, the Panel noted that the press release was used on 30 January and that the undertaking was dated 3 February. Thus Allergan had not breached its undertaking in Case AUTH/2460/11/11 and no breach of the Code was ruled in each case. These rulings were not appealed.

Notwithstanding the fact that in Case AUTH/2460/11/11 Allergan had been reported to the Code of Practice Appeal Board, the Panel once again decided firstly in Case AUTH/2487/3/12 and subsequently in Case AUTH/2489/3/12 to report the company to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. The continued breaches of undertaking raised serious questions about the company's procedures and commitment to complying with the Code. The Panel noted that in Case AUTH/2460/11/11 the Appeal Board had required an audit of Allergan's procedures in relation to the Code to be carried out by the Authority and had also decided that the company should be publicly reprimanded for successive breaches of its undertakings.

In considering the appeals the Appeal Board noted that Moers-Carpi *et al* demonstrated in a head-to-head comparison that 20 units of Vistabel was as effective as 30 units of Bocouture in the treatment of glabellar lines. The Appeal Board noted, however,

that the recommended starting dose for both products according to their SPCs was 20 units and it thus queried the choice of doses. The Appeal Board noted Allergan's submission on this point. Moers-Carpi *et al* did not examine the efficacy of the starting dose of Bocouture and whether this dose would have achieved the same clinical result as 30 units. In that regard the Appeal Board noted that once muscle saturation had occurred, any increase in dose would not produce any increase in effect.

The Appeal Board considered that the press release at issue gave an accurate account of Moers-Carpi *et al*. Given that both study medicines were botulinum toxins, the Appeal Board considered that many clinicians would assume that the difference in dosing to achieve a similar therapeutic effect meant that Vistabel (20 units) was more potent than Bocouture (30 units). In that regard the Appeal Board noted the following quotation from the press release: 'We are pleased to see further evidence for the efficacy of Vistabel and consider that this study provides further clarity that Vistabel and the Merz unit doses are not interchangeable in clinical practice'.

The Appeal Board noted that the press release did not refer to the relative potency of Vistabel and Bocouture but nonetheless, in its view, the inevitable implication was that Bocouture, unit for unit, was less potent than Vistabel. In the Appeal Board's view, in this particular context, ie a direct comparison of two botulinum toxins dosed in units, clinicians might well take efficacy and potency to mean one and the same. The discussion of Moers-Carpi *et al* in isolation in the press release did not represent the balance of the evidence with regard to the relative efficacy of Vistabel and Bocouture. Given the implied claim that Bocouture was less potent than Vistabel, the Appeal Board considered that the press release was sufficiently similar to the point at issue in Cases AUTH/2346/8/10 and AUTH/2460/11/11 for it to be covered by the undertaking in Case AUTH/2346/8/10. Thus the press release now at issue breached a previous undertaking. The Appeal Board upheld the Panel's rulings. The Appeal Board further considered that Allergan's successive breaches of undertaking was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's rulings of breaches of Clause 2. The appeals were unsuccessful.

The Appeal Board noted that it was important for the reputation of the pharmaceutical industry that companies understood the importance of their undertakings and took the necessary action to comply with them. The Appeal Board questioned Allergan's conduct and attitude in this regard and decided that the company should be publicly reprimanded for its successive failures to comply with its undertakings. These two cases taken together represented the fourth breach of undertaking. Allergan's conduct was completely unacceptable. The Appeal Board also decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of Allergan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted at the same time as the re-audit required in Case

AUTH/2460/11/11 which was scheduled to take place in August 2012. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary including pre-vetting of promotional material.

On receipt of the August 2012 audit report the Appeal Board was disappointed at the lack of progress demonstrated. However the company appeared to have taken action including setting time frames for the bulk of the processes and work to be completed by the end of 2012. The Appeal Board was concerned that the amendments to some of the standard operating procedures (SOPs) had not been finalized. The Appeal Board noted that there were plans to significantly change the company structure and the interim country manager would be replaced in 2013. A UK medical director was due to be appointed. The Appeal Board considered that Allergan should be re-audited in January 2013 at which point it expected there to be significant improvement.

Upon receipt of the January 2013 audit report, the Appeal Board noted that although Allergan had made progress, further improvement was necessary. The Appeal Board noted that one key change in senior personnel would take place shortly and another in due course. Given that further improvement was required, the Appeal Board considered that Allergan should be re-audited in September 2013. Upon receipt of the next audit report, the Appeal Board would decide whether further sanctions were necessary.

Upon receipt of the September audit report, the Appeal Board noted that Allergan had made progress since the re-audit in January. The company had undergone four audits since April 2012. It was important that the progress shown in the September 2013 audit was continued and maintained. Every opportunity should be taken for improvement. The Appeal Board noted that Allergan needed to ensure that it updated its processes in good time to reflect the 2014 Code and that relevant staff were trained on the new Code. Allergan provided details of its plans to implement the recommendations in the audit report. On the basis that this work was completed, the Appeal Board decided that no further action was required.

Merz Pharma UK Ltd alleged that Allergan UK Limited had breached undertakings given in previous cases in relation to the promotion of Vistabel/Botox (onabotulinumtoxinA). Merz marketed Bocouture/Xeomin (incobotulinumtoxinA).

The matters were taken up with the Director acting as the complainant as the PMCPA was responsible for ensuring compliance with undertakings.

COMPLAINT

Merz stated that again Allergan had made disparaging, misleading and unbalanced claims about the comparative potency/clinical efficacy of Bocouture/Xeomin and Vistabel/Botox.

The claims at issue were consistent with previous breaches of undertaking, most recently

Case AUTH/2460/11/11 together with Cases AUTH/2183/11/08 and AUTH/2346/8/10. These cases clearly demonstrated a pattern of behaviour by Allergan that showed a flagrant disregard for the Code and associated sanctions. Merz considered that Allergan's actions in this case were covered by the same undertakings as in the previous cases. A breach of Clause 25 was alleged.

The material at issue in Case AUTH/2487/3/12 was an article in *Cosmetic News*, March 2012. The article 'Dosages for botulinum toxins are not interchangeable says study' was written as if it were an Allergan press release. Its tone and style together with the direct quotations from Allergan employees clearly inferred that this was a promotional statement provided by Allergan. It therefore fell under Clause 1.2 as an 'activity undertaken by a pharmaceutical company or with its authority'.

The material at issue in Case AUTH/2489/3/12 was an article in the *International Journal of Aesthetic and Anti-Ageing Medicine (PRIME)* March 2012. Merz submitted that as this was a UK-based publication with many of its readers in the UK, it was covered by the Code. The article entitled 'BTX-A Dosing Not Interchangeable' was written as if it were an Allergan press release (and was substantially similar to what Merz considered was another breach of undertaking (Case AUTH/2487/3/12) in the March 2012 edition of *Cosmetic News*). Merz stated that the tone and style of the article together with the direct quotations from Allergan employees clearly inferred that this was a promotional statement provided by Allergan. It therefore fell under Clause 1.2 as an 'activity undertaken by a pharmaceutical company or with its authority'.

Merz noted that the articles summarised Moers-Carpi *et al* (2011) (a poster presented at the 7th European Masters in Anti-Aging Medicine (EMAA), September 2011) that was the subject of the breach of undertaking in Case AUTH/2460/11/11. This was a non-peer reviewed poster authored by two Allergan employees together with a third author. The articles made claims about the potency of Vistabel compared with Bocouture – a comparison which had been the subject of Cases AUTH/2460/11/11 and AUTH/2346/8/10 – building the case with the intention of implying that Bocouture was less potent than Vistabel.

Merz considered that the design of this study was open to significant question as there was no control arm and unmatched doses of each product were used, making potency comparison difficult. In Case AUTH/2460/11/11 the Panel concluded that the use of Moers-Carpi *et al* data alone did not reflect the balance of evidence and Merz alleged that this was also the case with the *Cosmetic News* and *PRIME* articles in question. The data had not been used in the context of the summaries of product characteristics (SPCs) recommendations for either product of the same starting dose of 20U. Additionally the data was not contextualised, there was no reference to the regulatory approved study data (Sattler *et al* 2010) which demonstrated non-inferiority between the two medicines at a 1:1 dosing conversion ratio.

Merz noted that the articles in *Cosmetic News* and *PRIME* did not refer to the established position by Carruthers *et al* (2005) which compared four doses of Botox in eighty females with moderate to severe glabellar frown lines at the doses of 10U, 20U, 30U and 40U. The study demonstrated that Botox showed no measurable clinical difference between 20U and 30U; the authors concluded that there 'were no statistically significant differences among the three higher-dose groups'. It was postulated that in most patients 20U was sufficient to saturate the local nerve endings so that additional dosing had little or no incremental clinical effect.

Merz alleged that the crafting of both articles, the selective use of data and what could only be a deliberate omission of the clearly established regulatory position to imply reduced potency/effectiveness of Bocouture compared with Vistabel was both cynical and clearly in breach of previous multiple undertakings made by Allergan.

In summary Merz noted that Allergan had been ruled in breach for suggesting that Xeomin (the same pharmaceutical product as Bocouture) was less potent than Botox (the same pharmaceutical product as Vistabel) in Case AUTH/2183/11/08. Following this Allergan gave an undertaking not to use this or similar claims. This undertaking was breached twice in Cases AUTH/2335/7/10 and AUTH/2346/8/10 and Allergan gave yet another undertaking. In Case AUTH/2460/11/11 Allergan was again ruled in breach of an undertaking relating to product potency claims in relation to Bocouture. Within only one month of the outcome of Case AUTH/2460/11/11, Allergan had briefed a third party to promote the same unbalanced data that it was not able to promote directly.

Merz was concerned that Allergan was relentless in its pursuit of the message that the Bocouture and Xeomin units were less potent than the Vistabel and Botox units against all the clinical evidence and the view of the Medicines and Healthcare products Regulatory Agency (MHRA) and the wider European regulators. Furthermore, in Case AUTH/2487/3/12 Merz noted that it was able to comment on an article in the March issue of *Cosmetic News* up until 23 February. The publication had thus not gone to press by this date which was some time after the ruling for Case AUTH/2460/11/11. Merz insisted on a corrective statement in the publication to help to rectify the clearly misleading statements that had previously been published.

In Case AUTH/2487/3/12 Merz identified an article in *Cosmetic News* that was a verbatim quotation of the one at issue in Case AUTH/2489/3/12. It would be reasonable to conclude that both articles had come from the same Allergan press release. In Case AUTH/2489/3/12 Merz additionally submitted that furthermore Allergan had repeatedly demonstrated that it had no intention to complying with undertakings. In Case AUTH/2460/11/11 Allergan was reported to the Code of Practice Appeal Board. Merz believed that full and fair competition was healthy but it was important to ensure that physicians received accurate and truthful information and were able to make informed decisions about products.

When writing to Allergan, the Authority asked it to respond in relation to Clause 2 in addition to Clause 25 cited by Merz.

RESPONSE

Allergan stated that Moers-Carpi *et al* was presented at the 7th EMAA Congress (held in Paris, September 30-1 October 2011) and also at the International Master Course on Aging Skin (IMCAS) Congress (held in Paris, 26-29 January 2012). A press release regarding the new study was drafted for use at EMAA. However, the press release was not finalised and was not used at EMAA. Subsequently, the draft press release was finalised and approved (examined) on Zinc (UK/0762/2011).

The press release covered the presentation of the new study at EMAA. The clear message from the title and the text was that unit doses of botulinum toxins, as with all biologicals, were not interchangeable. There was no suggestion or implication of sub-potency of the Merz toxin.

Allergan considered the presentation of this new study at a scientific congress was a newsworthy event. These new data from a large (n=220) randomised, double blind, peer reviewed equivalence study directly challenged the hypothesis that botulinum toxins were interchangeable at a 1:1 dose ratio. The study compared 20 units of Vistabel with 30 units of Bocouture. The basis for this study was the investigators' clinical experience of the relative effectiveness of the different products in clinical practice, the differences seen in the different reference LD50 assays and the different dose ranging data that were available.

Allergan submitted that these data were not inconsistent with the findings of the Merz non-inferiority studies or indeed the Bocouture SPC. The study confirmed that unit doses of botulinum toxins were not interchangeable. The study clearly challenged the basis for any claims of equivalence or a 1:1 conversion ratio made by Merz.

Allergan noted that subsequent to EMAA, Moers-Carpi *et al* re-presented their data at IMCAS. Allergan's PR agency contacted the editors of Cosmetic News and PRIME on 30 January, following IMCAS, and provided a copy of the press release (UK/0762/2011). Neither the agency nor Allergan's PR team had any further correspondence or calls with either journal on this matter or received any page proofs. Neither Allergan nor its PR agency were offered the chance to comment on the articles. An email chain to confirm the history of the events outlined above was provided.

Allergan did not consider it had breached its undertakings given in Cases AUTH/2335/7/10 and AUTH/2346/8/10. It provided a press release covering the details of a new study with a clear message of non-interchangeability not sub-potency of Merz toxin. The press release was reviewed with the above cases in mind and wording was amended to remove reference to potency. Data from a new study was provided with a clear take away message of non-interchangeability.

Regarding Case AUTH/2460/11/11, Allergan informed the PMCPA of its intention not to appeal the rulings on 3 February 2012.

Allergan accepted that there were a number of areas for improvement with respect to the handling of press releases and interactions with its PR agency. Allergan had instigated further training and a review of procedures regarding review, approval and release of press and media materials.

Allergan denied breaches of Clauses 25 and 2.

PANEL RULING

The Panel noted that Allergan had been notified of the outcome of Case AUTH/2460/11/11 on 26 January 2012, four days before it sent a press release about the Moers-Carpi *et al* (2011) data to Cosmetic News and PRIME; the subsequent articles were published in the March edition of the journals. In Case AUTH/2460/11/11, Allergan was again ruled to have breached undertakings with regard to claims about the relative potency of its botulinum toxin vs that of the Merz product. One of the matters at issue was specifically about the emphasis given to the Moers-Carpi *et al* results in the relative absence of other data. Allergan accepted the rulings of breaches of the Code and signed the relevant undertaking on 3 February 2012; there was no reference in the undertaking to any other material that could not be withdrawn due to the passing of copy deadlines. The Panel noted the submission from Merz in Case AUTH/2487/3/12 that it had been given up until 23 February to comment on an article which was to be published in the March edition of Cosmetic News. Allergan submitted that after it had sent the press release on 30 January, it had not had any further contact with Cosmetic News and PRIME or been offered the chance to comment on the articles. The Panel noted that Allergan's PR agency had provided the press release following its contact with the editors of Cosmetic News and PRIME (30 January) in the period when Allergan, having received the notification of the Panel's rulings of breaches in Case AUTH/2460/11/11 (26 January) and report to the Code of Practice Appeal Board, would be deciding whether to accept or appeal those rulings (due 3 February). The Panel also noted that the press release was examined and signed on 25 January which was whilst Allergan was awaiting the outcome of a relevant complaint, Case AUTH/2460/11/11.

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the publisher/journalist and not on the content of the article itself. The articles which appeared in the March editions of Cosmetic News and PRIME reproduced large sections of Allergan's press release. The press release was headed 'New study provides further evidence that dosing for botulinum toxins are not interchangeable'; the sub-heading read 'Head to head study launched at international aesthetics congress further reinforces need for awareness of the different doses for two botulinum toxin type A products'. The press release ended with a quotation from one of the authors of Moers-Carpi *et al*, an Allergan employee; 'We are pleased

to see further evidence for the efficacy of Vistabel and consider that this study provides further clarity that Vistabel and the Merz unit doses are not interchangeable in clinical practice’.

The Panel noted that in Case AUTH/2460/11/11 both parties had submitted more information than above. The Panel thus noted the following paragraph from its ruling in point 1 of that case:

‘The Panel noted that there appeared to be no standard assay method for the two [botulinum toxin] preparations. The SPCs for Botox/Vistabel referred to Allergan Units/vial and the Bocouture/Xeomin SPCs referred to LD50 units per vial. The Xeomin SPC stated that due to differences in the LD50 assay, these units were specific to Xeomin and were not interchangeable with other botulinum toxin preparations. All of the SPCs stated that as the botulinum toxin units differed from product to product, doses recommended for one product were not interchangeable with those for another. The Bocouture SPC, however, stated that comparative clinical study results suggested that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900kD) [Botox/Vistabel] were of equal potency. The Xeomin 50 units SPC contained the equivalent statement but added ‘when used with a dosing conversion ratio of 1:1’. In this regard the Panel noted that Sattler *et al* (2010) demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin (n=277) to Botox/Vistabel (n=93) in the treatment of glabellar frown lines. The SPCs for Bocouture and Vistabel stated identical recommended unit doses for the treatment of moderate to severe glabellar frown lines, ie five injections each of 4 units. The Bocouture SPC stated that the dose might be increased to up to 30 units if required by the individual needs of the patient.’

The Panel also noted that a representative’s use of copies of the Moers-Carpi *et al* poster had been at issue in point 2 of Case AUTH/2460/11/11. The Panel thus noted the following relevant paragraphs from its ruling on that matter:

‘The Panel noted that the Vistabel sales aid (ref UK/0775/2011) provided by Allergan as the only promotional item that referred to Moers-Carpi *et al* was entitled ‘Not all toxins are Vistabel’. The front cover included the statement ‘Vistabel unit doses are not interchangeable with other preparations of botulinum toxins’. One page in the sales aid was headed ‘Head-to-head data review of glabellar lines’ beneath which was boxed text with a very brief description of Sattler *et al* and a more detailed description of Moers-Carpi *et al*. Subsequent pages of the sales aid detailed the results of Moers-Carpi *et al* with the use of a bar chart and graph. The back page of the material included the claim ‘A recently conducted equivalence study confirms that unit doses of Vistabel and Merz toxin are not interchangeable in clinical practice’ which was referenced to Moers-Carpi *et al*. There was no reference on the back page to the Sattler *et al*

non-inferiority study which showed that 24 units of Bocouture/Xeomin was non-inferior to 24 units of Botox/Vistabel in the treatment of glabellar lines. There was no mention of the statement in the Bocouture SPC that clinical data suggested equal potency.

There was no complaint about the sales aid. However, the Panel considered it was relevant to the allegation that the customer was left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

The Panel noted that the Moers-Carpi *et al* poster was not available for representatives to distribute; if customers asked for a copy the representatives had to ask medical information to send a copy or receive a copy themselves in a sealed envelope for onward transmission to the customer. Allergan had acknowledged that three customers had asked the representative for a copy of the poster. In that regard the Panel noted Allergan’s submission that the requests were unsolicited. In the Panel’s view, the emphasis on the Moers-Carpi *et al* data within the sales aid meant that any request for a copy of the poster which was prompted by a representative’s discussion of that data was a solicited request for the poster.

The Panel noted that it was impossible to know what the representative had said to any of the three customers about the poster or whether the representative had used the sales aid. However, the Panel considered that, given the content of the sales aid, on the balance of probabilities, the representative had used the Moers-Carpi *et al* poster to inform the health professional that in order to achieve the same clinical outcome in the treatment of glabellar lines 20 units of Vistabel was needed vs 30 units of Bocouture ie unit for unit, Bocouture was less potent than Vistabel.’

The Panel noted that in Case AUTH/2346/8/10 Allergan had been ruled in breach of its undertaking given in Case AUTH/2183/11/08 in that an impression was given that Botox was more potent than Xeomin and this was inconsistent with the product SPCs and available clinical data. Breaches of Clauses 2, 9.1 and 25 were ruled.

Turning to the cases now at issue, Cases AUTH/2487/3/12 and AUTH/2489/3/12, the Panel noted that the press release in question (UK/0762/2011 Date of preparation Dec 2011) was itself undated. It had been examined on 25 January 2012 according to the Zinc certificate. The press release was only about the Moers-Carpi *et al* data. The results of that study had not been set within the context of the recommended doses for Vistabel and Bocouture according to their SPCs, the statement in the Bocouture SPC that comparative clinical study results suggested that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900kD) [Botox/Vistabel] were of equal potency and the clinical results of Sattler *et al* which showed that 24 units of Bocouture/Xeomin was non-inferior to 24 units of Botox/Vistabel in the treatment of glabellar lines.

The Panel did not consider that the discussion of Moers-Carpi *et al*, in isolation, in the press release represented the balance of the evidence with regard to the relative efficacy of Vistabel and Bocouture. In the Panel's view, the press release implied that in order to achieve the same clinical outcome in the treatment of glabellar lines, 20 units of Vistabel was needed vs 30 units of Bocouture, ie unit for unit, Bocouture was less potent than Vistabel. In that regard the Panel considered that the press release was sufficiently similar to the point at issue in Cases AUTH/2346/8/10 and AUTH/2460/11/11 for it to be covered by the undertaking in Case AUTH/2346/8/10. Thus the press release now at issue breached an undertaking previously given. A breach of Clause 25 was ruled in each case. These rulings were appealed by Allergan.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2 in each case. These rulings were appealed by Allergan.

The Panel was concerned that Allergan stated that it had reviewed the press release in relation to the outcome of Cases AUTH/2335/7/10 and AUTH/2346/8/10 and that the press release had been sent out during the time Allergan would be considering whether to appeal yet another breach of undertaking ruled by the Panel in Case AUTH/2460/11/11. Given the seriousness of the situation, the Panel considered that Allergan should have taken urgent action and considered not using the press release until it had decided whether to appeal Case AUTH/2460/11/11, particularly as the form of undertaking required withdrawal of any similar material. Allergan could have contacted the editors of Cosmetic News and PRIME following its provision of the undertaking in Case AUTH/2460/11/11. However, the Panel noted that the press release was used on 30 January and that the undertaking was dated 3 February. Thus Allergan had not breached its undertaking in Case AUTH/2460/11/11 and no breach of Clause 25 was ruled in each case. These rulings were not appealed.

The Panel noted that in case AUTH/2487/3/12, Merz had requested that Allergan publish a corrective statement to help rectify the misleading impression given in the March edition of Cosmetic News. Corrective statements were a sanction available only to the Code of Practice Appeal Board.

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The Panel noted its rulings in this case that Allergan had again breached its undertaking with regard to claims about the relative potency of its botulinum toxin vs that of the Merz product. Cases AUTH/2346/8/10 and AUTH/2460/11/11 had been ruled in breach of Clauses 2, 9.1 and 25. Notwithstanding the fact that in Case AUTH/2460/11/11 Allergan had been reported to the Code of Practice Appeal Board, the Panel once again decided firstly in Case AUTH/2487/3/12 and subsequently in Case AUTH/2489/3/12 to report the company to the Appeal Board in accordance with

Paragraph 8.2 of the Constitution and Procedure. The continued breaches of undertaking raised serious questions about the company's procedures and commitment to complying with the Code. The Panel noted that in Case AUTH/2460/11/11 the Appeal Board had required an audit of Allergan's procedures in relation to the Code to be carried out by the Authority and had also decided that the company should be publicly reprimanded for successive breaches of its undertakings.

APPEAL BY ALLERGAN

Allergan noted that the Panel had ruled that it had breached the undertaking given in Case AUTH/2346/8/10 following publication of two articles based on its press release.

By way of background, Allergan reiterated that Moers-Carpi *et al* was presented at the 7th EMAA Congress in October 2011 and at the IMCAS Congress in January 2012.

Allergan submitted that it had originally drafted a press release about the Moers-Carpi *et al* study with the intention of issuing it in connection with EMAA. However, the press release was not finalised in time and so it was subsequently issued in connection with IMCAS, although it erroneously referenced EMAA. Allergan submitted that the intention of the study and the press release, as evidenced by the clear message from the title and the text of the release, was that unit doses of botulinum toxins were not interchangeable, a point strongly made in the labels of all approved botulinum toxins. There was no suggestion or implication of sub-potency of the Merz toxin, as this was not the intention of the release.

Allergan reiterated that the launch of this study at EMAA was newsworthy. These new data from a large (n=220), randomised, double blind, peer reviewed equivalence study directly challenged Merz's claim that botulinum toxins were interchangeable at a 1:1 dose ratio. The study compared 20 units of Vistabel with 30 units of Bocouture. The basis for this study was the investigators' clinical experience of the relative effectiveness of the different products in clinical practice, the differences seen in the different reference LD50 assays and the different dose ranging data that was available.

Allergan further reiterated that these data were not inconsistent with the findings of the Merz non-inferiority studies or the SPC for Bocouture at the time (dated 29 June 2010). In fact, the only thing with which the study was inconsistent was the claim that the products were equivalent or interchangeable at a 1:1 dose ratio. While not revealed to the PMCPA, Merz had known for some time that this language would be removed from the posology section of its label but continued to rely upon that language. However, the updated Bocouture SPC (dated 6 March 2012) had removed the language and was thus not inconsistent with the conclusion of Moers-Carpi *et al*. The study confirmed that unit doses of botulinum toxins were not interchangeable and clearly challenged the basis for any claims by Merz of equivalence or a 1:1 conversion ratio.

Dr Moers-Carpi presented the study and its conclusions at IMCAS. Allergan again noted that its PR agency (CCA) contacted the editor of Cosmetic News on 30 January, following IMCAS, and provided a copy of the press release. Neither CCA nor Allergan had any further correspondence or calls with Cosmetic News on this matter and they did not receive any page proofs. Neither Allergan nor CCA were offered the chance to comment on the article. The email chain to confirm the history of the events outlined above was provided.

Allergan again submitted that it had not breached its undertakings with respect to Case AUTH/2346/8/10 (or Case AUTH/2335/7/10). Allergan provided a press release covering the details of a new study with a clear message of non-interchangeability, not sub-potency of Merz's toxin.

Allergan submitted that the press release was intended to announce an important new and newsworthy study which shed further light on what should have been an incontrovertible fact, that unit doses of botulinum toxin type A products were not interchangeable.

Allergan submitted that its goal was not to state or imply sub-potency. Indeed, claiming or implying that it took 30 units of Xeomin to get 20 units of Botox efficacy was not only not its goal in the study or press release, but was inconsistent with its view on this matter which it had stated throughout this, and other cases. These products were not interchangeable, regardless of dose conversion ratio. They had separate profiles, they were separate products and had different efficacy and safety margins all of which were indication specific. They acted differently. The last thing Allergan wanted was a fixed dose ratio implied regarding these products. Allergan submitted that its press release was clear in that regard and the study, and quotation from the lead investigator and Dr Fulford-Smith, confirmed that unit doses of botulinum toxins were not interchangeable.

Allergan submitted that the presentation of Moers-Carpi *et al* without reference to either the Bocouture SPC or the Merz non-inferiority study (Sattler *et al*) was not unbalanced. This study and the claims made by Allergan were not inconsistent or out of line with any of the other available data from Merz, Allergan or Ipsen/Galderma. All the available data, including Moers-Carpi *et al*, confirmed that unit doses were not interchangeable. This new study was not designed to, and could not be used to, establish a fixed dose conversion between products.

In Allergan's view, the Panel had accepted the concept that there was an established 1:1 conversion ratio between Botox/Vistabel and Xeomin/Bocouture and in this regard had been misled by Merz.

Allergan knew that changes to the Bocouture and Xeomin 50U SPCs were approved on 6 March 2012 following Allergan's communication to the Pharmacovigilance Working Party (PhVWP) highlighting the potential patient safety concerns with the Bocouture and Xeomin 50U SPC wording. A summary of these changes was provided. However,

in summary, in the Bocouture SPC any reference to equal potency had been removed. In Section 4.2 of the Xeomin 50U SPC the statement regarding 1:1 dosing ratio had been removed. Section 5.1 of the SPC still contained information regarding its non-inferiority studies but this was specifically in relation to patients with blepharospasm or cervical dystonia. As previously established, non-inferiority studies did not support claims of equivalence.

Allergan submitted that it had not undertaken this appeal lightly; it understood the serious nature of its position, especially given the very recent PMCPA audit. Allergan was completely committed to compliance with the Code and understood that it had to address significant issues with respect to process, integration and teamwork, resources and training. Allergan further accepted that there were a number of areas for improvement with respect to the handling of press releases and interactions with its PR agency. Allergan had instigated further training and a review of its procedures regarding review, approval and release of press and media materials.

However, Allergan did not believe that it had breached its undertaking by implying or stating that Merz's toxins were sub-potent. Allergan had provided information on a new study which reflected the balance of evidence and the clearly established fact that unit doses of botulinum toxin type A products were not interchangeable.

Allergan did not accept the Panel's ruling of breaches of Clauses 2 and 25.

COMMENTS FROM MERZ

Merz noted that in Case AUTH/2183/11/08 the Panel ruled that, on the balance of probabilities, an Allergan representative had claimed that there was a difference in potency between Botox and Xeomin, which was inconsistent with the guidance on prescribing in the respective SPCs. The Panel also found that the supporting promotional material examined was misleading and unsubstantiated and did not support the rational use of medicine. The Panel determined that the training materials issued in association with the promotional material did not maintain high professional standards.

Merz noted that in Case AUTH/2460/11/11 the Panel again reached a similar conclusion, that the selective use of data to convey a message of sub-potency of Xeomin/Bocouture to Botox/Vistabel (in the form of the Moers-Carpi *et al* data) did not reflect the balance of evidence and was misleading. Specifically the data had not been used in the context of the SPC recommendations for either product with the same starting dose of 20 units. Additionally the data had not been contextualised without reference to the regulatory approved study data (Sattler *et al*) which demonstrated non-inferiority between the two medicines at a 1:1 dosing ratio. Allergan was notified of this view on 26 January 2012.

On 30 January Allergan issued a press release announcing new data which demonstrated that 20 units of Vistabel were equivalent to 30 units of Xeomin. Merz alleged that the new data was the

same data by Moers-Carpi *et al* subject of the ruling in Case AUTH/2460/11/11, it was again selectively presented without context. The Panel ruled in Cases AUTH/2487/3/12 and AUTH/2489/3/12 regarding the press release that:

- The results of the study had not been set within the context of the recommended doses for Vistabel and Bocouture according to the SPCs
- The Panel did not consider that the discussion of Moers-Carpi *et al*, in isolation in the press release represented the balance of evidence with regard to the relative efficacy of Vistabel and Bocouture
- In the Panel's view the press release 'implied that Bocouture was less potent than Vistabel'. In this regard that Panel considered that the press release was sufficiently similar to the point at issue in Cases AUTH/2460/11/11 and AUTH/2346/8/10
- In addition, the Panel referred to the serial breaches in Cases AUTH/2335/7/10, AUTH/2346/8/10, AUTH/2460/11/11 and the seriousness of the situation associated with the lack of urgent action taken by the company with respect to these new cases

Whilst Merz accepted that because it had not signed the undertaking in Case AUTH/2460/11/11 until 3 February Allergan had avoided a breach of this undertaking by a technicality, Merz fully supported the Panel's ruling that the persistent use of isolated data out of context and in conflict with the regulatory head-to-head clinical studies and SPC dosage guidance, was in breach of the undertaking given in Case AUTH/2183/11/08.

Merz noted that Xeomin/Bocouture and Botox/Vistabel had been compared at a 1:1 dose conversion ratio across numerous indications, in large registration standard studies designed with advice from the regulatory authorities. In these studies Xeomin/Bocouture had consistently been found to be non-inferior to Botox/Vistabel at a 1:1 dose conversion ratio with no significant differences being observed between any of the primary and secondary efficacy variables measured.

Merz submitted that it was an inconvenient truth for Allergan that a 1:1 ratio made switching from Botox/Vistabel to Xeomin/Bocouture relatively straightforward and cost comparisons more obvious. This represented a clear commercial threat for Allergan.

Allergan stated its position on the 1:1 conversion ratio very clearly in its appeal when it stated;

'These products were not interchangeable, regardless of the conversion ratio. They had separate profiles, they were separate products and had different efficacy and safety margins all of which were indication specific. They acted differently. The last thing Allergan wanted was a fixed dose ratio implied regarding these products.'

Merz took this statement point by point and submitted the following:

- 1 *'these products were not interchangeable, regardless of the conversion ratio'* – Merz submitted that Xeomin/Bocouture had been demonstrated non-inferior to Botox/Vistabel at a 1:1 dosing ratio, and this was reflected in the product SPC dosing guidance (the fact that units of potency were product specific was inconsequential to this comparison).
- 2 *'They had separate profiles, they were separate products and had different efficacy and safety margins all of which were indication specific'* – Merz submitted that Xeomin/Bocouture and Botox/Vistabel had consistently been shown to have comparable efficacy and similar safety profiles with no significant difference between onset of action, peak effect, duration of effect and diffusion through muscle being observed across all indications assessed (Sattler *et al*, Roggenkamper *et al*, 2006, Benecke *et al* 2009, Jost *et al* 2005).
- 3 *'They acted differently. The last thing Allergan wanted was a fixed dose ratio implied regarding these products'* – Merz noted that both Xeomin/Bocouture and Botox/Vistabel were botulinum toxin type A, they both originated from the same Hall strain of Clostridium botulinum and they both blocked cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine. This similarity was reinforced by the near identical descriptions of their mode of action in Section 5.1 of their respective SPCs.

Merz stated that what could be observed by Allergan's conduct, and was very clearly articulated in its appeal, was that it could not accept 'a fixed dose ratio being implied regarding these products'. One could presume it would represent an unacceptable commercial threat.

Merz alleged that in the face of this compelling clinical data Allergan had sought to leverage a statement indicating that the different products had different assays to assess their preclinical potency and elevate it to a level above that of the dosing guidance in the respective SPC's and the robust clinical data on which that guidance was issued. Merz was confident that this was not the objective of the PhVWP in the drafting of the 'units of potency' statement that botulinum toxin products should be rendered incomparable in the clinical setting.

Allergan's argument that the phase IV Moers Carpi *et al* data, co-authored by an employee of Allergan, challenged the validity of previous head-to-head comparisons was flawed. Moers Carpi *et al* demonstrated that there was no benefit in using a higher dose of Bocouture (30 units) vs a lower dose of Botox (20 unit) which was why both products had an initial dose recommendation of 20 units. As the dosing arms were not matched, no useful comparison of potency could be made. Or to put it another way, if a man could drown in 10 feet of one brand of mineral water as quickly as he could in 20 feet of another brand of mineral water did that make the first brand of mineral water twice as dangerous

or beyond comparison? No, it did not. To draw out Allergan's conclusion it had used the finding of the paper to communicate that toxins were not interchangeable it was a fair challenge to ask how they interpreted the findings of its paper (Curruthers *et al*) which found no significant difference between 20 and 30 units of Botox in treating glabellar frown lines.

In Allergan's appeal it submitted that Moers Carpi *et al* directly challenged Merz's claim that botulinum toxins were interchangeable at a 1:1 dose ratio. Merz alleged that it did not. Used in isolation it represented the most recent in a series of breaches of undertaking which it appeared should not stop until Allergan accepted that Xeomin/Bocouture had been demonstrated non-inferior to Botox/Vistabel at a 1:1 dosing ratio. Allergan was on record in its appeal that it would not accept this fact.

Allergan stated that Merz had withheld pending changes in the Bocouture SPC to the Panel and implied that the recent changes in the wording of the SPC might be associated with the Moers-Carpi *et al* data. Merz submitted that the matter at hand should be assessed against the position at the time of the breach, without mitigation for future events but was happy to address the matter.

Merz stated that it was common following the approval of a new product licence in Europe, for regulatory harmonisation to occur. Following the pan-European approval of the 50U Xeomin vial throughout 2011, an updated SPC for Xeomin and Bocouture was developed in conjunction with the regulators. The final version was approved by the MHRA over a month after the release of Allergan's press briefing document on Moers-Carpi *et al* and implemented by Merz within a week of receipt.

Merz stated that as a result of the harmonisation process the Xeomin statement of 1:1 comparable potency was moved from Section 4.2 (Posology and method of administration) to Section 5.1 (Pharmacodynamic properties) of the SPC where a clearer reference to the comparative studies was made. At the same time the more appropriate use of the term 'efficacy', rather than 'potency' was used to describe the study data.

Merz noted that Section 4.2 of the revised Xeomin 50 unit SPC (March 2012 revision) stated: '... Study results also suggest that Xeomin and this comparator product [Botox] have a similar efficacy and safety profile in patients with blepharospasm or cervical dystonia when used in a dosing conversion ratio of 1:1 ...'.

Merz stated that the harmonisation process was on-going and would result in further SPC updates for Xeomin 100 unit and Bocouture 50 unit. Merz submitted that Moers Carpi *et al* did not feature in its discussions with the MHRA on this matter. Similarly Merz did not believe that the body of data on this matter had changed, that the respective SPCs still reflected the clinical situation and that the SPCs still supported the 1:1 dosing schedule in their dosing guidance.

In summary, Merz supported the Panel's rulings and its approach to ensuring compliance to previous undertakings.

APPEAL BOARD RULING

The Appeal Board noted that the press release at issue had to be considered in relation to the statements which were in the Merz SPCs (Bocouture and Xeomin 50U) when it was issued and not those subsequently approved on 6 March 2012. All the SPCs for botulinum toxins included a statement that botulinum toxin units were not interchangeable from one product to another.

The Appeal Board noted that Moers-Carpi *et al* demonstrated in a head-to-head comparison that 20 units of Vistabel was as effective as 30 units of Bocouture in the treatment of glabellar lines. The Appeal Board noted, however, that the recommended starting dose for both products according to their SPCs was 20 units and it thus queried the choice of doses. The Appeal Board noted Allergan's submission on this point. Moers-Carpi *et al* did not examine the efficacy of the starting dose of Bocouture and whether this dose would have achieved the same clinical result as 30 units. In that regard the Appeal Board noted that once muscle saturation had occurred, any increase in dose would not produce any increase in effect.

The Appeal Board considered that the press release gave an accurate account of Moers-Carpi *et al*. Given that both study medicines were botulinum toxins, the Appeal Board considered that many clinicians would assume that the difference in dosing to achieve a similar therapeutic effect meant that Vistabel (20 units) was more potent than Bocouture (30 units). In that regard the Appeal Board noted the following quotation from the press release: 'We are pleased to see further evidence for the efficacy of Vistabel and consider that this study provides further clarity that Vistabel and the Merz unit doses are not interchangeable in clinical practice'.

The Appeal Board noted that the press release did not refer to the relative potency of Vistabel and Bocouture but nonetheless, in its view, the inevitable implication was that Bocouture, unit for unit, was less potent than Vistabel. In the Appeal Board's view, in this particular context, ie a direct comparison of two botulinum toxins dosed in units, clinicians might well take efficacy and potency to mean one and the same. The discussion of Moers-Carpi *et al* in isolation in the press release did not represent the balance of the evidence with regard to the relative efficacy of Vistabel and Bocouture. Given the implied claim that Bocouture was less potent than Vistabel, the Appeal Board considered that the press release was sufficiently similar to the point at issue in Cases AUTH/2346/8/10 and AUTH/2460/11/11 for it to be covered by the undertaking in Case AUTH/2346/8/10. Thus the press release now at issue breached a previous undertaking. The Appeal Board upheld the Panel's rulings of breaches of Clause 25. The Appeal Board further considered that Allergan's successive breaches of undertaking was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Appeal Board upheld

the Panel's rulings of breaches of Clause 2. The appeals were unsuccessful.

The Appeal Board noted that it was important for the reputation of the pharmaceutical industry that companies understood the importance of their undertakings and took the necessary action to comply with them. The Appeal Board questioned Allergan's conduct and attitude in this regard and decided that the company should be publicly reprimanded for its successive failures to comply with its undertakings. These two cases taken together represented the fourth breach of undertaking. Allergan's conduct was completely unacceptable. The Appeal Board also decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of Allergan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted at the same time as the re-audit required in Case AUTH/2460/11/11 which was scheduled to take place in August 2012. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary including pre-vetting of promotional material.

FURTHER APPEAL BOARD CONSIDERATION

Although the Appeal Board was disappointed, on receipt of the August 2012 audit report, at the lack of progress demonstrated, the company appeared to have taken action including setting time frames for the bulk of the processes and work to be completed by the end of 2012. The Appeal Board was concerned that the amendments to some of the standard operating procedures (SOPs) had not been finalized. The Appeal Board noted that there were plans to significantly change the company structure. The Appeal Board considered that Allergan should be re-audited in January 2013 at which point it expected there to be significant improvement.

Upon receipt of the January 2013 audit report, the Appeal Board noted that although Allergan had made

progress, further improvement was necessary. The Appeal Board noted that one key change in senior personnel would take place shortly and another in due course. Given that further improvement was required, the Appeal Board considered that Allergan should be re-audited in September 2013. Upon receipt of the next audit report, the Appeal Board would decide whether further sanctions were necessary.

Upon receipt of the September audit report, the Appeal Board noted that Allergan had made progress since the re-audit in January. The company had undergone four audits since April 2012. It was important that the progress shown in the September 2013 audit was continued and maintained. Every opportunity should be taken for improvement. The Appeal Board noted that Allergan needed to ensure that it updated its processes in good time to reflect the 2014 Code and that relevant staff were trained on the new Code. Allergan provided details of its plans to implement the recommendations in the audit report. On the basis that this work was completed, the Appeal Board decided that no further action was required.

Complaint received (Case AUTH/2487/3/12)	6 March 2012
Complaint received (Case AUTH/2489/3/12)	12 March 2012
Appeal Board Consideration	28 June, 11 October 2012, 6 March, 15 October 2013
Undertakings received	17 July 2012
Interim case report first published	2 December 2012
Case completed	15 October 2013

GLAXOSMITHKLINE v NAPP

Flutiform leavepieces

GlaxoSmithKline complained about two Flutiform (fluticasone/formoterol) leavepieces issued by Napp. GlaxoSmithKline marketed Seretide (fluticasone/salmeterol). Flutiform and Seretide were both indicated for the treatment of asthma. The leavepieces included a comparison of Flutiform pressurized metered dose inhaler (pMDI) with Seretide Evohaler (pMDI).

The response from Napp is detailed below.

GlaxoSmithKline alleged that the claim 'Comparable clinical efficacy' (between Seretide and Flutiform) did not reflect the evidence and misled the reader. The claim was based upon a 12 week, open label study using low and medium doses of both products in patients aged 18 years or older (Bodzenta-Lukaszyk *et al* 2011). The study demonstrated non-inferiority of forced expiratory volume in the first second (FEV1) as a primary outcome and discontinuation due to lack of efficacy as a secondary outcome. GlaxoSmithKline submitted that the study did not support the claim.

The Panel noted that the primary endpoint of Bodzenta-Lukaszyk *et al* was non-inferiority based on mean FEV1. Secondary endpoints included discontinuations due to lack of efficacy, time to onset of action, peak expiratory flow rates and other lung function parameters, amount of rescue medication use, asthma symptom scores, sleep disturbance due to asthma, daily corticosteroid doses and asthma exacerbations. The study demonstrated that Flutiform was comparable to Seretide in terms of the primary endpoint and certain secondary efficacy endpoints. Flutiform was superior to Seretide in terms of time to onset of action.

Whilst noting that FEV1 was a fundamental efficacy measurement, the Panel considered the broad unqualified claim 'comparable efficacy' implied more than a measurement of FEV1. In this regard the Panel noted that the secondary outcome data in Bodzenta-Lukaszyk *et al* (2011a) showed that Flutiform and Seretide were similar in a number of additional relevant efficacy measurements.

The Panel noted that Flutiform was not recommended for use in children younger than 12 and that high dose Flutiform should not be used in adolescents. Seretide 25/50mcg, however, could be prescribed from the age of 4 and from the age of 12 children could be treated with all three doses of Seretide.

The Panel noted that the heading to the page at issue in leavepiece 1 read 'Why should I prescribe Flutiform instead of Seretide Evohaler?' The Panel

considered that many readers would already be familiar with the Seretide Evohaler. The Panel considered that the broad, unqualified claim 'Comparable clinical efficacy' implied that Flutiform could be used in all of those patients for whom Seretide might be prescribed and that there was robust comparative clinical data in relation to all doses and patient populations and that was not so. The Panel noted that there was some comparative efficacy data but considered that insufficient information about the study had been provided to enable the reader to accurately interpret the claim which was consequently misleading and incapable of substantiation. The Panel noted that the first page of the leavepiece stated that Flutiform was 'combined for the first time for asthma maintenance therapy for patients 12 years and older (low and medium strengths); adults (all strengths)'. However, this statement was in a small font size such that, in the Panel's view, it would be missed by many readers. The Panel did not consider that the statement was prominent enough to set the rest of the leavepiece in context. In the Panel's view the statement on the first page did not negate the otherwise misleading impression given by the claim 'Comparable clinical efficacy'. Breaches of the Code were ruled.

The Panel noted that in leavepiece 2 a preceding bullet point explained that Flutiform 50/5mcg and 125/5mcg were licensed for use in patients aged 12 years and above. The immediate subheading to the claim in question made it clear that patients had mild to moderate-severe persistent asthma. However, it had not been made clear that only medium and low doses of Seretide Evohaler had been compared in patients aged 18 years or over. The Panel also noted its comments above about the secondary clinical endpoints in Bodzenta-Lukaszyk *et al*. On balance, the Panel considered that the rulings made in relation to leavepiece 1 also applied to leavepiece 2; further breaches of the Code were ruled.

GlaxoSmithKline alleged that the cited reference (Mansur 2008 published in full as Mansur and Kaiser 2012) did not support the claim 'The efficacy and tolerability of Flutiform were sustained for up to 12 months'. The positioning of the claim directly below the claim for comparable efficacy misled readers into assuming that 'comparable efficacy' had been demonstrated over 12 months.

The Panel noted that Mansur and Kaiser was an open label study in which mild to moderate-severe asthmatics age 12 years and over were treated twice daily with low or medium dose Flutiform for 6 or 12 months. The primary and secondary objectives were the long-term safety and efficacy of Flutiform.

The study demonstrated statistically significant improvements overall and for both treatment groups for each efficacy assessment. Flutiform demonstrated a good safety and efficacy profile over the 12 month study period.

The Panel noted that the claim 'The efficacy and tolerability of Flutiform were sustained for up to 12 months' appeared immediately beneath the claim for comparable clinical efficacy with Seretide. The Panel considered that the positioning of the claims was such that the second would inevitably be read in light of the first and thus readers would infer that comparable clinical efficacy with Seretide was demonstrated for up to 12 months and that was not so. The claim was misleading on this point as alleged and a breach of the Code was ruled.

GlaxoSmithKline noted the question 'Why should I prescribe flutiform instead of Seretide Evohaler' and submitted that Flutiform was not a suitable substitute for all patients who were eligible for Seretide. Seretide 50 Evohaler was licensed from 4 years and older whilst Seretide 125 and 250 Evohalers were licensed from age 12 years and older. Flutiform 50 and 125 were licensed from 12 years and older and Flutiform 250 was licensed from age 18 years and older. Unlike Seretide, Flutiform contained ethanol and was only licensed for use with the AeroChamber Plus spacer device; Seretide was licensed for use with both the Volumatic and AeroChamber Plus spacer devices.

GlaxoSmithKline alleged that the omission of clinically important differences when advising that Flutiform was an alternative to Seretide was misleading; it was not fair, balanced or objective and created confusion between the two products. Prescribers were not informed of the unsuitability of Flutiform for some patients prescribed Seretide. This might encourage off-label prescribing and usage and compromise patient safety.

The Panel noted that Flutiform was not a suitable substitute for younger patients who could be treated with Seretide Evohaler. The Panel again noted that many readers would already be familiar with Seretide. The Panel considered that in the absence of information to the contrary, readers would assume that Flutiform could be substituted for Seretide Evohaler in all circumstances and that was not so. The information about Flutiform's licensed indication, in relatively small print, was insufficient to negate the unequivocal impression given by the claim. The Panel considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

GlaxoSmithKline stated that although 'Faster onset of action' was presented as the key differentiator between Flutiform and Seretide Evohaler it had not been established that a shorter time to onset of action was of value in a controller medicine. Furthermore, Napp did not provide any clinical evidence to substantiate the clinical relevance of the claim.

GlaxoSmithKline noted that in leaviepiece 1 the claim 'Faster onset of action' appeared on the same page and next to the bold claim 'flutiform is licensed for maintenance therapy and not for acute symptom relief'. A claim for a faster onset of action was typically synonymous with a reliever (or SMART [Symbicort Maintenance and Reliever Therapy] therapy) and could, potentially, lead to inappropriate off-label use of Flutiform inconsistent with its SPC and compromise patient safety.

GlaxoSmithKline maintained that Napp had failed to substantiate the clinical relevance of the claim or give information such that readers could assess the clinical relevance of a faster onset of action with this controller medication. The juxtaposition of claims in leaviepiece 1 misled the reader and potentially encouraged Flutiform to be misused and prescribed off-licence.

The Panel noted both parties' submissions about the clinical relevance of the claim. In particular, the Panel noted the studies submitted by Napp indicated overall that onset of action was of clinical interest and relevance for a maintenance therapy. The claim was not misleading or incapable of substantiation on this point. No breach of the Code was ruled.

The Panel noted that alongside the bullet points, including that at issue above, was an image of a Flutiform pMDI beneath which was the prominent claim 'flutiform is licensed for maintenance therapy and not for acute symptom relief'. The Panel did not consider that the juxtaposing of the claim 'Faster onset of action' and the description of its licensed use for maintenance therapy misled the reader as alleged or promoted it in a manner that was inconsistent with its marketing authorization. It was clear that Flutiform was licensed for maintenance therapy. The Panel further noted that the claim was within the context of 'Why should I prescribe flutiform instead of Seretide Evohaler?'. The Panel again noted that prescribers would be familiar with Seretide and know that it was only indicated as a maintenance therapy. No breach of the Code was ruled.

GlaxoSmithKline stated that the data cited in support of claims for cost-effectiveness most closely resembled a cost-minimisation analysis which required robust evidence for clinical equivalence with respect to patient outcomes. There was, however, no randomised, double-blind head-to-head study which compared Seretide and Flutiform. The only comparison between the two was Bodzenta-Lukaszyk *et al* and, as noted above, the primary endpoint of the trial was non-inferiority of FEV1. High doses of Seretide and Flutiform had not been compared and studies of high dose were an essential prerequisite to establish comparable safety with any degree of certainty.

GlaxoSmithKline alleged that the cost-effectiveness claims were not fair, accurate or balanced and that

the cost comparisons made were misleading and not substantiated by the cited reference.

The Panel noted that the claims at issue were referenced to data on file which Napp described as a cost-minimisation study. Only acquisition costs were compared. The Panel noted each party's submission on whether Bodzenta-Lukaszyk *et al* demonstrated comparable efficacy and thus whether a cost-minimisation study was the appropriate analysis. In particular, the Panel noted the study was a non-inferiority study and had not been designed to demonstrate equivalence. The Panel also noted its rulings and comments above about the study in relation to patients' ages, doses and asthma severity. The Panel queried whether a cost-minimisation analysis was therefore appropriate.

The Panel noted that cost-minimisation studies were a legitimate activity; any claims derived therefrom had to clearly reflect the analysis and not otherwise be misleading. The Panel considered that a reader would expect the claim 'cost-effectiveness' in the absence of further qualification, to mean more than a simple comparison of acquisition costs. In each leavepiece subsequent and distinct sections discussed comparative acquisition costs thus compounding the impression that 'cost-effectiveness' was different and broader than a simple cost comparison.

The Panel considered that the claims 'Improved cost-effectiveness' in leavepiece 1, '... a cost-effective treatment for asthma management' and '... a cost-effective treatment choice ...' in leavepiece 2, each implied that matters broader than acquisition cost had been compared. In addition the Panel noted its concerns about the cost-minimisation study and its reliance on Bodzenta-Lukaszyk *et al* as set out above. The claims were thus each misleading and incapable of substantiation. Breaches of the Code were ruled.

GlaxoSmithKline noted the claims 'cost-effective treatment for asthma management' and 'a cost-effective treatment choice when ICS/LABA [inhaled corticosteroid/long-acting B2-agonist] combination inhalers were being considered at Step 3 or 4 of the SIGN/BTS [Scottish Intercollegiate Guidelines Network/British Thoracic Society] guidelines'. Napp data on file was cited in support of both claims. GlaxoSmithKline submitted that there were other products and devices available for 'asthma management' and at 'Step 3 or 4 of the BTS/SIGN guidelines'. These had not been included within the leavepiece or within the Napp data on file. Some of these products cost less than Flutiform.

GlaxoSmithKline submitted that the leavepiece advised switching. Switching inhalers was a complex process and required follow-up of the patient to ensure asthma control was maintained and that the patient continued to use the inhaler properly.

No evidence was presented in the leavepiece to demonstrate that asthma control was maintained

when/if patients were switched. Consequently the claims for potential annual savings did not take into account the costs associated with the necessary additional clinical interactions required with patients when they had their medicines changed or the potential costs associated with the risk of any resultant exacerbations.

In addition, the data presented were stratified by age; however, there were many patients who could not be switched to Flutiform who had not been considered eg patients who used a Volumatic spacer or those who were unable to use inhalers containing ethanol. Furthermore, the Napp data on file did not include the full range of products and devices and thus could not substantiate the above claims.

The Panel noted that the heading of leavepiece 2 was a broad unqualified claim that Flutiform was a cost-effective treatment for asthma management when compared with all other relevant products. The comparison was not limited to that with Seretide Evohaler. The Panel noted its general comments above. The Panel considered that the heading was misleading as alleged and a breach of the Code was ruled.

The Panel noted that the claim 'flutiform provides the clinician with a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Step 3 or 4 of the SIGN/BTS guidelines' was the sole bullet point in a section headed 'Rationale for flutiform'. In the Panel's view the claim implied that Flutiform was a cost-effective choice when compared with all other ICS/LABA combination inhalers used at Steps 3 or 4 of the guidelines. It was not limited to a comparison with the Seretide Evohaler as alleged and was misleading in this regard. Breaches of the Code were ruled.

The Panel noted that the table within the section headed 'Potential savings per annum' compared the cost savings, based on acquisition costs if 25%, 50% or 75% of patients on Seretide Evohaler 50, 125 and 250 were switched to Flutiform. In the Panel's view the table did not advocate switching *per se* as alleged by GlaxoSmithKline. It merely set out the potential savings based on acquisition costs in the event of a switch to the Seretide Evohaler. In the Panel's view, the basis of the comparison was clear and was not misleading. No breach of the Code was ruled.

GlaxoSmithKline stated that in leavepiece 1 a claim of cost-effectiveness lay adjacent to a cost comparison of the three different strengths of Seretide Evohaler and Flutiform. Cost-effectiveness compared with Evohaler had not been demonstrated as discussed above. Given that cost-effectiveness had not been demonstrated, the juxtapositioning of this statement next to a cost comparison table that was itself not balanced, was misleading.

The cost comparison table only compared Flutiform to Evohaler. GlaxoSmithKline noted that alternative maintenance therapies were available at Step 3 and 4 of the BTS/SIGN guidelines. Furthermore, the

omission by Napp of the Seretide Accuhaler prices, particularly the high strength, appeared deliberate to conceal the fact that the Seretide 500 Accuhaler was less expensive than Flutiform 250/10mcg. In inter-company dialogue, Napp submitted that the Seretide Evohaler was the most appropriate comparator because clinical data vs Seretide Evohaler had been presented within leavepiece 1. GlaxoSmithKline disagreed with Napp's position and noted that the appropriate information referenced to Bodzenta-Lukaszyk *et al*, for the mid/low doses comparisons was missing from the cost comparison table. By so doing, the reader was unaware that the rationale for this cost comparison was based solely upon non-inferior FEV1 results over a 12 week period in adults.

Whilst GlaxoSmithKline acknowledged that Napp's rationale for only directly comparing the two products, when other products were available, was because head-to-head data existed, it must be clearly acknowledged that data only existed for the low and medium doses of the inhaler, in 18 year olds and in an open label study that did not include severe patients.

As previously highlighted, Seretide Evohaler and Flutiform differed in many aspects; licensed age ranges, alcohol content and spacer device usage. None of these had been made clear within leavepiece 1 which implied that all patients could be prescribed Flutiform instead of Seretide Evohaler. Clearly, this was not the case and Napp was obliged to present these important differences in a fully transparent and balanced way.

In summary, GlaxoSmithKline alleged that the cost comparison table was misleading, not accurate, fair or balanced.

The Panel noted its rulings above in relation to the claim 'Improved cost-effectiveness'. That claim was a bullet point beneath a prominent subheading and page heading. It was not 'next to' the cost comparison table on the facing page as GlaxoSmithKline alleged, nor was it within that table's immediate visual field. The Panel, whilst noting its ruling above, did not consider that the position of the claim 'Improved cost-effectiveness' on page 1 in relation to the table on page 2 was, in itself, misleading as alleged. No breach of the Code was ruled.

The Panel considered that the basis of the comparison in the table was clear, the acquisition costs of the three strengths of flutiform were compared with those of the three strengths of Seretide Evohaler. There was no implication that all patients could be prescribed Flutiform instead of Seretide Evohaler, as alleged. Nor was it unacceptable to directly compare the acquisition costs of products if the basis of that comparison was abundantly clear. The table was not misleading as alleged. No breach of the Code was ruled.

GlaxoSmithKline stated that the leavepiece compared both clinical and economic aspects of Seretide Evohaler and Flutiform. The claim, 'flutiform has a simple dosing schedule administered

as 2 puffs, twice daily', appeared directly below the table at issue above.

In a comparative leavepiece designed to state why Flutiform should be prescribed instead of Seretide, the juxtaposition of the above statement directly below a comparative table implied that Seretide's dosing schedule was not simple or not as simple as Flutiform. This was not the case as the dosing schedules for the two inhalers were exactly the same.

To describe a dosing schedule as 'simple' was both promotional and a hanging comparison and therefore required substantiation. Alternative, simpler dosing schedules for asthma were available eg Seretide Accuhaler, one puff twice a day. Napp did not provide evidence to demonstrate that patients viewed a dosing schedule of two puffs twice a day as being simple but, in inter-company dialogue, advised that 'It ... is a plain statement of fact in terms of the dosing schedule for Flutiform being simple'.

GlaxoSmithKline alleged that within comparative tables and leavepieces between Seretide and Flutiform, claims of a simple dosing schedule for Flutiform when the dosing schedules were the same was misleading. Furthermore, when simpler dosing schedules were available, a claim of simple was not accurate or balanced and was misleading.

The Panel noted that the claim in question appeared in small print beneath the comparative table at issue above which comprised most of the page. The Panel considered that the claim would be considered by readers in the context of the overall comparative message of the page and thus it implied that Seretide Evohaler did not have a simple dosing schedule and that was not so. Seretide Evohaler had the same dosing schedule as Flutiform. The claim was misleading in this regard and incapable of substantiation. Breaches of the Code were ruled.

The Panel considered that the claim indirectly compared the dosing schedule of Flutiform with Seretide Evohaler. The Panel therefore did not consider the claim was a hanging comparison as alleged. Nor was it misleading because other products with simpler dosing schedules were available as alleged by GlaxoSmithKline. The Panel considered that the claim in question was not misleading on these points and no breach of the Code was ruled.

GlaxoSmithKline submitted, given the totality of the multiple issues raised and unresolved through extensive inter-company dialogue, that collectively the two leavepieces disparaged Seretide. In addition, given the seriousness and number of breaches, the failure to maintain high standards and the potential to encourage Flutiform prescribing outside the marketing authorization and impact upon patient safety, the two leavepieces constituted additional breaches of the Code including Clause 2.

The Panel noted its rulings above of breaches and no breaches of the Code. Whilst some comparisons had been considered misleading, the Panel did not

consider that they went beyond that and disparaged Seretide Evohaler. No breach of the Code was ruled.

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

Although noting its rulings above, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular disapproval of a company's material or activities. No breach of Clause 2 was ruled.

GlaxoSmithKline appealed the ruling of no breach of Clause 2. The company subsequently tried to withdraw its appeal but was prevented from doing so by the Constitution and Procedure. The Appeal Board noted that the Panel had ruled a breach of the Code in that high standards had not been maintained. The Appeal Board was concerned about the breaches of the Code and the possible, theoretical adverse consequences of some of the claims on patient safety but considered that, on balance, the circumstances did not warrant a breach of Clause 2 and it upheld the Panel's ruling of no breach of Clause 2. The appeal was thus unsuccessful.

GlaxoSmithKline UK Limited complained about two Flutiform (fluticasone propionate/formoterol) leavepieces issued by Napp Pharmaceuticals Limited which, *inter alia*, compared Flutiform with GlaxoSmithKline's product Seretide (fluticasone/salmeterol). Flutiform was a pressurised metered dose inhaler (pMDI) and the leavepieces compared Flutiform with Seretide Evohaler also a pMDI. Leavepiece 1 (ref UK/FLUT-11050) was a four page, A5 leaflet. The front page was headed with a search engine box 'Fluticasone and formoterol in a fixed-dose combination'. The search returned one result, depicted in the highlighted box below, 'Flutiform'. Leavepiece 2 (ref UK/FLUT-11023a) was a double sided, A4 document headed 'flutiform (fluticasone propionate/formoterol fumarate) inhaler as a cost-effective treatment for asthma management'.

Flutiform was indicated in the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid [fluticasone] and a long-acting β_2 -agonist [formoterol]) was appropriate. Seretide was similarly indicated in the regular treatment of asthma where the use of a combination product was appropriate.

Both parties provided extensive background information which is summarised below.

Summary of the background information provided by GlaxoSmithKline

GlaxoSmithKline explained that there were two main types of medicines to treat asthma: relievers and controllers.

Relievers contained a short-acting β_2 -agonist (SABA), were used on an 'as required' basis to quickly relieve

symptoms of an asthma exacerbation and reverse bronchoconstriction.

Controllers, which contained a combination of a long-acting β_2 -agonist (LABA) and an inhaled corticosteroid (ICS), were used on a daily basis for the maintenance therapy of asthma so patients could achieve and maintain control of their symptoms. Seretide and Flutiform were both combination products.

Seretide was available in two different devices, a metered dose inhaler (MDI), the Evohaler and a dry powder inhaler, the Accuhaler. Flutiform was available only as a MDI.

GlaxoSmithKline explained that both Seretide and Flutiform were used at Steps 3 to 5 of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) Guidelines. The BTS/SIGN Guidelines defined the current standard of care in the UK and advised that the therapy goal was to achieve and maintain control. UK and international treatment guidelines stated that to demonstrate if asthma control was achieved in patients either in a clinical trial or within clinical practice, effective treatments must demonstrate that control of both lung function and clinical symptoms could be achieved. It was not appropriate to specify a single endpoint for the assessment of asthma control, and clinical efficacy studies should use endpoints which captured both lung function and clinical symptoms. GlaxoSmithKline provided a table of data summarising the parameters for asthma control as defined in various guidelines.

GlaxoSmithKline explained that the Gaining Optimal Asthma Control (GOAL) study (Bateman *et al* 2004) was a 1 year, stratified, randomised, double-blind, parallel-group study which compared the efficacy and safety of individual, pre-defined, stepwise increases of Seretide with Flixotide (fluticasone propionate, GlaxoSmithKline, monotherapy). Within the GOAL study Seretide achieved and maintained guideline defined control over 12 months. GlaxoSmithKline provided a table which compared the primary endpoints of the GOAL study, Bodzenta-Lukaszyk *et al* (2011a) and Bodzenta-Lukaszyk *et al* (2011b).

Currently there were no randomised, double-blind, head-to-head studies which compared Seretide Evohaler with Flutiform to investigate if asthma control as defined by UK and international guidelines could be achieved. The only comparative study was a 12 week, open label, non-inferiority study which investigated the low and mid doses of both Seretide Evohaler and Flutiform in adults over the age of 18 years, using a spacer device (Bodzenta-Lukaszyk *et al* 2011a). The primary outcome, ie non-inferiority of the forced expiratory volume in the first second (FEV1) over a 12 week period in the full analysis set, was demonstrated. Of the secondary outcomes, the study demonstrated non-inferiority of discontinuations of study medication, and Flutiform was seen to have a faster onset of action. The actual times to onset of action were not stated in the published paper although this difference diminished over the 12 week treatment period. The patients'

assessment of study medication significantly favoured Seretide (Odds ratio 0.495 CI 0.289, 0.848), and trends in favour of Seretide were seen for rescue medication use but this did not reach significance for the published per-protocol population. Importantly, this head-to-head study did not demonstrate non-inferiority between Flutiform and Seretide for any of the clinical measures of asthma control.

Bodzenta-Lukaszyk *et al* (2011a) did not include adolescents and the high doses were not compared. In addition, only less severe patients were included as evidenced by observed exacerbation rates of 14% over 12 weeks in patients taking Flutiform compared with exacerbation rates of 35.1% over 8 weeks seen when Flutiform was compared with its individual components (Bodzenta-Lukaszyk *et al* 2011b). In both studies, numerically more patients taking Flutiform experienced severe exacerbations than those patients taking Seretide or GlaxoSmithKline's fluticasone propionate monotherapy. The current head-to-head data were not of sufficient duration or adequately powered to determine whether this result might represent a discriminatory effect between the two products due to the difference in steroid bioavailability.

Hochhaus and Kaiser (2011) suggested that Flutiform delivered 24-31% less fluticasone to the lungs than GlaxoSmithKline fluticasone monotherapy. However, importantly, the relationship between the bioavailability of Seretide and Flutiform had not been studied. GlaxoSmithKline noted, when salmeterol and fluticasone propionate were administered in combination by the inhaled route, as Seretide, the pharmacokinetics of each component were similar to those observed when the medicines were administered separately. The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varied between approximately 5-11% of the nominal dose depending on the inhalation device used (Seretide Evohaler summary of product characteristics (SPC)).

Summary of the background information provided by Napp

Napp explained that Flutiform was a new fixed-dose, inhaled combination of two well-known and established active substances: the ICS fluticasone propionate and the LABA formoterol fumarate. Fluticasone was the ICS in GlaxoSmithKline's Seretide combination inhaler, whilst formoterol was the LABA in AstraZeneca's Symbicort and Chiesi's Fostair.

Fluticasone propionate and formoterol fumarate had also been available for many years as individual inhaled monotherapies. The efficacy and safety profile of fluticasone was well established; it was a highly effective maintenance treatment for asthma, both as a single inhaler therapy and as the ICS component of the fixed-dose combination Seretide. The efficacy and safety profile of formoterol was also well established. Formoterol provided significantly more rapid bronchodilation than salmeterol and was comparable to that of the SABA salbutamol.

Although fluticasone and formoterol were available as monotherapies and in other combinations, until now they had not been available together in a single combination inhaler due to technical challenges in developing them as a room-temperature stable formulation.

Flutiform had been developed as 3 doses, based on the doses of ICS and LABA in the other available ICS/LABA products and the relevant monotherapies. The labelled dose strengths of fluticasone in Flutiform were the same as those in Seretide Evohaler. Seretide Evohaler and Flutiform devices also delivered similar doses of fluticasone as shown below.

	Flutiform pMDI	Fluticasone Salmeterol pMDI
Low dose (mcg)		
Labelled	50/5	50/25
Delivered	46/4.5	44/21
Medium dose (mcg)		
Labelled	125/5	125/25
Delivered	115/4.5	110/21
High dose (mcg)		
Labelled	250/10	250/25
Delivered	230/9.0	220/21

Flutiform was developed in a pressurised metered dose inhaler (pMDI) device with a dose counter. pMDIs were commonly used inhaler devices in the UK and were very familiar to health professionals and patients. pMDIs all operated in a similar fashion and with similar instruction.

Dry powder inhalation (DPI) devices, differed significantly in their operation from pMDIs and also from each other. Napp was concerned that GlaxoSmithKline did not clearly differentiate between its pMDI (Seretide Evohaler) and DPI (Seretide Accuhaler) inhalers in this complaint, when describing study results, or in its promotional materials.

It was relevant and important to understand why Flutiform pMDI was positioned against Seretide Evohaler pMDI and not Seretide Accuhaler DPI. Correspondence received from GlaxoSmithKline highlighted the issue of device switching (ie pMDI or DPI) with respect to loss of control and increased consultation time, highlighting that this was a concern for a switch from Seretide pMDI to Flutiform pMDI. GlaxoSmithKline cited Thomas *et al* (2009) as the key source of evidence for this. However, Thomas *et al* did not present data on a switch between pMDI treatments; the authors instead reported on the issues of switching between different devices ie between pMDI, DPI and breath-actuated device where there was a significant difference in operation and therefore potential for misuse leading to loss of asthma control and consultation time to train on the new device.

In the complaint GlaxoSmithKline cited objections to several Committee for Medicinal products for Human Use (CHMP) regulatory guidelines cited by Napp. Disappointingly, several of these arguments were not raised with Napp during inter-company dialogue, but they had been addressed (see Point 1 below).

In 2010 Napp submitted an application for Flutiform to the CHMP of the European Medicines Agency (EMA) via the decentralised procedure, with the UK Medicines and Healthcare Products Regulatory Agency (MHRA) as the reference member state. This was for three ascending doses of 50mcg fluticasone/5mcg formoterol, 125mcg fluticasone/5mcg formoterol and 250mcg fluticasone/10mcg formoterol per actuation via a pMDI suspension. The application was reviewed initially by 22 EU member states and thereafter (as with other recent applications) by the CHMP.

Regarding the decentralised procedure, Napp noted that the Flutiform regulatory submission was a full clinical dossier with a large and comprehensive clinical package, not an abridged application. The decentralised procedure started in June 2010. The indication sought was the regular treatment of asthma where the use of a combination product was appropriate: for patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2 -agonist. ['Step-up' indication]. Or for patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 -agonist. ['Switch' indication].

The clinical development programme for Flutiform evaluated efficacy and safety in the intended patient population. Efficacy was demonstrated by measures of both lung function and clinical symptoms. The total clinical programme comprised 18 completed studies and included almost 5,000 patients. The five pivotal Flutiform Phase III studies included approximately 2,500 patients and the safety database included over 1,900 Flutiform-treated patients. Studies included both adolescents (12 to 18 years) and adults. Section 5.1 of the Flutiform SPC also described limited paediatric information in children 4-12 years, but as was clear in Section 4.4, Flutiform was not for use in children under 12 years of age until further data was available.

The five pivotal clinical studies were designed to compare the efficacy and safety of Flutiform with its individual components administered separately and with its individual components administered together but inhaled from separate inhalers. Supportive studies compared the efficacy and safety of Flutiform with other combination therapies including a study which compared Flutiform with Seretide Evohaler pMDI (Bodzenta-Lukaszyk *et al* 2011a). It was not 'dismissed' by the CHMP as stated by GlaxoSmithKline, but was always considered to be a supporting study as the necessary guidelines indicated that the pivotal studies should be against the components of the combination. The development programme also assessed the efficacy and safety of Flutiform administered either with or without a spacer device and investigated the efficacy and safety of Flutiform across relevant subgroups. The CHMP and MHRA were consulted and they

supported the clinical study designs in the Phase III clinical development programme and the use of pre-dose FEV1 as the primary endpoint for efficacy in respect of corticosteroid effect. It was therefore clear that the relevant guidelines had been correctly followed.

As noted by GlaxoSmithKline, asthma control was one of two principal treatment goals in asthma management (the other being the reduction of exacerbation risk). It was a multidimensional concept incorporating symptoms, night-time awakenings, use of rescue medication, lung function and activity limitation.

Although pre-dose FEV1 was the main endpoint in the studies submitted, a number of other relevant patient symptom efficacy measures were captured as secondary endpoints. As such the application demonstrated that Flutiform provided improved asthma control compared with fluticasone monotherapy and a reduction in exacerbation risk. These data were reviewed and accepted by the EMA as evidence of the efficacy of Flutiform. The EMA also accepted extrapolation of an 8-12 weeks study duration to the longer term. The Flutiform European Public Assessment Report (EPAR) stated (page 9, paragraph 2):

'In conclusion, given the long-term predictive value of FEV1, given the static nature of FEV1 after 8 to 12 weeks of treatment, and given the pattern of the FEV1 data observed in the five pivotal studies, the CHMP considers there to be no reason to anticipate that the long-term exacerbation risk with Flutiform may exceed that with fluticasone propionate alone (the "Step-up" indication) or fluticasone propionate in combination with formoterol fumarate (the "Switch" indication). These conclusions based on an indirect assessment of future exacerbation risk are consistent with and support those based on a direct observation of exacerbation rates during the clinical studies.

The CHMP was of the view that clinical data generated over 6 to 12 months to further elucidate the level of asthma control and to further assess exacerbation rates seen with Flutiform compared with fluticasone propionate administered concomitantly with formoterol fumarate or administered alone, are not required.'

Furthermore, the EPAR (page 7, paragraph 6) noted:

'Turning to the available data in the Applicant's studies, for the "Step-up" comparison the odds of "any" exacerbation were 33% higher in fluticasone propionate- than Flutiform-treated patients ($p = 0.019$) whilst the annual exacerbation rate was 49% higher in fluticasone propionate- than Flutiform-treated patients ($p = 0.004$). These data were generated from the five pivotal 8- to 12-week studies and demonstrate the protective benefit of Flutiform against exacerbations compared with fluticasone propionate monotherapy. Published sources indicate that these treatment differences would at worst remain static and at best improve in favour of Flutiform over the longer-term.'

In conclusion, the CHMP had considered a large and comprehensive package of data and recommended Flutiform for the treatment of asthma where a combination product was appropriate:

‘Having considered the overall submitted data provided by the Applicant in writing and during the oral explanation, the CHMP concluded that the benefit-risk balance of Flutiform 50/5, 125/5 & 250/10 micrograms pressurised inhalation, suspension is positive under normal conditions of use.

The CHMP considered all concerns raised by the objecting member state to be adequately addressed and that they should not prevent the authorization of the product.

Therefore, the CHMP recommended the granting of the marketing authorization for Flutiform 50/5, 125/5 & 250/10 micrograms pressurised inhalation, suspension.’

Whilst Flutiform was a new combination pMDI inhaler there was still a significant amount of clinical data to support its use. The package included five pivotal studies of 8-12 weeks’ duration in both adults and adolescents; three supporting studies providing evidence including a paediatric study vs Seretide and two further supporting studies (one long-term and one vs monotherapies). Napp summarised the efficacy endpoints from the Phase III studies.

1 Claim ‘Comparable clinical efficacy’

The claim ‘Comparable clinical efficacy (p=0.007; open label)’ appeared as the second bullet point beneath the subheading ‘Prescribe flutiform instead of Seretide Evohaler because it can deliver:’ on the second page of leavepiece 1.

Beneath a subheading ‘An introduction to flutiform’, leavepiece 2 stated ‘Clinical trial data have shown that in patients with mild to moderate-severe persistent asthma: flutiform had comparable clinical efficacy to Seretide Evohaler (p=0.007; open label)’.

Both claims were referenced to Bodzenta-Lukaszyk *et al* (2011a).

COMPLAINT

GlaxoSmithKline explained that there were two published Flutiform studies; Bodzenta-Lukaszyk *et al* (2011a) (open label, randomised: Seretide Evohaler vs Flutiform) and Bodzenta-Lukaszyk *et al* (2011b) (double-blind, randomised: Flutiform vs fluticasone plus formoterol).

GlaxoSmithKline alleged that the claim ‘Comparable clinical efficacy’ (between Seretide and Flutiform) did not reflect the current available evidence, misled through exaggeration of the available data and was not sufficiently complete to enable the recipient to form their own opinion of the potential differences between the medicines.

Flutiform was a new combination inhaler that combined two medicines that had not been previously licensed for use in combination in an inhaler and were different from those seen in Seretide. This

new combination of medicines and excipients was delivered to the lung using different technological processes to the Seretide Evohaler resulting in different pharmacokinetic and pharmacodynamic properties.

The only evidence presented by Napp to substantiate ‘comparable clinical efficacy’ was a 12 week, open label study which examined the low and medium doses of both products in adult (aged 18 years or more) asthma patients. This study demonstrated non-inferiority of a lung function parameter (FEV1) as a primary outcome and discontinuation due to lack of efficacy as a secondary outcome. While FEV1 was, unarguably, an important measure of lung function it needed to be combined with clinical outcomes in order to demonstrate accepted criteria of clinical efficacy. Discontinuation due to study medication was not, *per se*, a recognised clinical measure of control and in this regard GlaxoSmithKline referred to the summary of clinical symptoms provided above in its background comments.

GlaxoSmithKline submitted that the evidence presented by Napp did not demonstrate or substantiate a claim of comparable clinical efficacy because:

i **The bioavailability of steroid component of Flutiform had not been studied but current evidence suggested that this was likely to be lower than that for Seretide so surrogate markers of clinical efficacy were inadequate.**

Seretide and Flutiform had different pharmacokinetic properties. This meant that to establish clinical equivalence, equivalence of clinical and lung function endpoints were required in adolescent and adult patients over six months.

The relationship between the bioavailability of Seretide and Flutiform had not been studied so was unknown. Hochhaus and Kaiser suggested that Flutiform delivered 24-31% less fluticasone to the lungs than GlaxoSmithKline fluticasone monotherapy. When salmeterol and fluticasone propionate were administered in combination, as Seretide, by the inhaled route, the pharmacokinetics of each component were similar to those observed when the medicines were administered separately.

Because of the different pharmacokinetic properties, it was therefore essential when claiming these two products had a comparable clinical effect, that robust clinical evidence was available to support such key claims and comparisons. GlaxoSmithKline alleged that Napp had failed to demonstrate adequate evidence to justify the claims.

ii **The clinical evidence presented to demonstrate comparable clinical efficacy was inadequate to substantiate this claim.**

GlaxoSmithKline submitted that Napp used FEV1 alone to demonstrate clinical comparability between Seretide Evohaler and Flutiform. Given that the two products contained different medicines and had different steroid bioavailability, this exaggerated the current evidence.

The CPMP/EWP/2922/01 guidance on the clinical investigation of asthma medicines defined the two categories of endpoints as lung function and clinical evidence. The guideline advised that 'for a new controller treatment ... an equal emphasis should be placed on lung function and the symptom based clinical endpoints'. For controller medicines it was also advised that 'for moderate and severe persistent asthma, symptom based endpoints are particularly important. These may include the frequency of exacerbations and an assessment of asthma control'. The evidence referenced by Napp did not include severe asthmatics and did not demonstrate non-inferiority for Flutiform compared with Seretide for any of the accepted parameters of clinical control.

In inter-company dialogue, Napp had justified the selection of study endpoints by reference to the CPMP/EWP/4151/00 Rev.1 Guideline that provided requirements for clinical documentation related to the application for marketing authorization through the abridged route (ie was for the demonstration of therapeutic equivalence between two products that were essentially the same). GlaxoSmithKline believed that reference to this guideline was incorrect because:

- Flutiform did not meet the requirements for application for a marketing authorization through the abridged route when compared with Seretide
- Flutiform differed from Seretide in terms of active ingredients, excipients and delivery technology
- Lung deposition and pharmacokinetic differences between Seretide and Flutiform had not been studied. Current evidence suggested that steroid bioavailability was likely to be substantially lower for Flutiform when compared with Seretide
- The EPAR stated that the CHMP dismissed Bodzenta-Lukaszyk *et al* (2011a) as not being relevant to the application for marketing authorization.

In addition, if the CPMP/EWP/4151/00 Rev.1 Guideline was relevant, the Seretide/Flutiform head-to-head data differed significantly from the guideline recommendations. Thus, any conclusions based on reference to this guideline exaggerated the available evidence. The following examples demonstrated where the evidence presented by Napp deviated from the guideline recommendations for demonstrating therapeutic equivalence through an abridged marketing authorization application:

- A double-blind, double-dummy design was recommended
- 'For new fixed combination products with no approved fixed combination reference product the inclusion of an additional treatment arm in which patients would receive the ICS component alone is necessary' (Section 6.2.3.3)
- Adolescents required separate study (Section 9)
- The study would need to show a significant statistical dose response relationship (Section 6.2.3.3)
- Bronchial challenge response endpoints were recommended (Section 6.2.2.2, 6.2.3.1).

For the reasons stated, if regulatory guidance documents were referenced, GlaxoSmithKline believed that guidance document CPMP/EWP/2922/01

(Note for guidance on the clinical investigation of medicinal products in the treatment of asthma, November 2002) was the more suitable reference for the selection of the necessary study endpoints required to demonstrate clinical efficacy most appropriately.

The CPMP/EWP/2922/01 guidance on the clinical investigation of asthma medicines defined the two categories of endpoints as lung function and clinical evidence; the guideline advised that 'for a new controller treatment ... an equal emphasis should be placed on lung function and the symptom based clinical endpoints'. For controller medications it was also advised that 'for moderate and severe persistent asthma, symptom based endpoints are particularly important. These may include the frequency of exacerbations and an assessment of asthma control'. The evidence cited by Napp did not include severe asthmatics and did not demonstrate non-inferiority for Flutiform compared with Seretide for any of the accepted parameters of clinical control.

This guidance also advised that 'Claims for chronic treatment should be supported by the results from randomised, double-blind, parallel, controlled clinical trials of at least six months' duration' and 'equal emphasis should be placed on lung function and the symptom based clinical endpoint'. GlaxoSmithKline believed that this was especially relevant when comparability claims were based upon head-to-head data for two products that were different in many respects.

In inter-company dialogue Napp also referenced a ATS/ERS 2009 consensus statement to justify the extrapolation of FEV1 non-inferiority to infer clinical comparability. The consensus statement advised that FEV1 was one of the main spirometric parameters relevant to asthma. GlaxoSmithKline acknowledged that FEV1 was one of the fundamental lung function parameters and needed to be measured within a clinical trial and also in clinical practice. However, the consensus statement also advised:

'Symptoms and lung function represent different domains of asthma and they correlate poorly over time in individual patients, so both need to be monitored by clinicians assessing control in clinical practice.'

'Based on experience with anti-inflammatory therapy, it is often assumed that future risk of exacerbations will directly parallel changes in current clinical control. However these two aspects are not necessarily concordant ... with combination ICS/LABA.'

'Given that the goals of asthma treatment relate to both the achievement of good control and the minimization of future risk, it is not appropriate to specify a single primary endpoint for the assessment of asthma control. Studies of clinical efficacy and effectiveness should use appropriate endpoints which capture both aspects of asthma control.'

'Symptom scores in adults and children generally have moderate or weak correlations with other asthma outcomes, including static lung function, PEF variability, airway reactivity, and air inflammation,

consistent with the fact that these represent different domains of asthma control.'

'It is not appropriate to specify a single primary endpoint for the assessment of asthma control.'

'Many studies have reported low to moderate relationships between airflow limitation (measure by FEV1), respiratory symptoms and health related quality of life.'

It was therefore unfair and flawed to represent the limited evidence available and extrapolate FEV1 to conclude that Seretide and Flutiform were clinically comparable. The aim of combination inhaled therapies was to ensure good asthma control irrespective of the product prescribed. Where, as argued, the products were sufficiently different, claims of comparability based on the use of surrogate parameters which were short-term markers of lung function were clearly inadequate, inappropriate and ill advised. To do so was disparaging and sought to reduce confidence in the detailed evidence generated over time by the research-based pharmaceutical industry.

iii The patient selection was inadequate to allow extrapolation to all asthma severities and licensed age ranges.

As evidenced by the low exacerbation rates observed in the Seretide/Flutiform head-to-head study, severe patients were not included. In Bodzenta-Lukaszyk *et al* (2011a) exacerbation rates of 14% were seen over 12 weeks in patients taking Flutiform compared with 35.1% seen over 8 weeks in patients taking Flutiform in Bodzenta-Lukaszyk *et al* (2011b). In both studies, numerically more patients taking Flutiform experienced severe exacerbations than those patients taking Seretide or GlaxoSmithKline fluticasone propionate. The current head-to-head data were not of sufficient duration nor had sufficient power to determine whether this result might represent a discriminatory effect between the two products due to the differences in steroid bioavailability.

Adolescent patients had also not been included in the head-to-head study (Bodzenta-Lukaszyk *et al* (2011a)). Napp indicated that the selection of patients for demonstration of clinical comparability could be referenced to CPMP/EWP/4151/00 Rev.1. Although GlaxoSmithKline disputed Napp's use of this guideline to justify its promotional approach, it did nevertheless advise that adolescents should be included in asthma clinical studies.

In contrast, the clinical efficacy of Seretide in adolescents and adults had been proven in the GOAL study which demonstrated that the majority of patients (62-75%) previously symptomatic on ICS were able to achieve guideline-defined control with the regular use of Seretide. Guideline defined control was defined by achieving two or more of the following criteria:

- Rescue salbutamol use ≤ 2 days and ≤ 4 occasions per week
- Symptoms score > 1 on ≤ 2 days per week
- $\geq 80\%$ predicted morning PEF every day.

and all of the following criteria:

- No night-time wakening due to asthma
- No exacerbations
- No emergency visits
- No treatment-related adverse effects enforcing a change in asthma therapy.

The GOAL study was one of the pivotal studies in respiratory medicine and defined the standard of care for asthma patients. The claim that Flutiform and Seretide had comparable clinical efficacy implied that the above outcomes would be achieved with Flutiform. The current evidence did not substantiate that claim.

iv The doses studied could not be extrapolated to infer clinical comparability of all doses.

Only the mid and low doses of Seretide Evohaler and Flutiform had been compared. In inter-company dialogue Napp maintained that these results could be extrapolated to indicate comparability of high doses. Napp justified the appropriateness of comparing the high dose strength and stated that in vitro dose linearity had been proven as part of the marketing authorization, and referred to CPMP/EWP/4151/00 Rev.1 Guidelines and stated:

'If dose linearity is demonstrated in vitro when different dose strengths of a known active substance are sought it may be sufficient to establish therapeutic equivalence clinically with only one strength of the active substance. It is usually appropriate to study the lowest strength, at more than one dose level, to enhance the sensitivity of the study.'

GlaxoSmithKline was not aware that dose linearity of Flutiform compared with Seretide had been studied, however, as previously discussed; CPMP/EWP/4151/00 Rev.1 specifically provided guidance for establishing equivalence between two products that were essentially the same. These guidelines were therefore not relevant as Flutiform was not a generic version of Seretide and the relative bioavailability of fluticasone was likely to be substantially lower in Flutiform. In addition, the Flutiform head-to-head study was powered to detect non-inferiority of the primary endpoint of FEV1, not equivalence.

Given the likely low bioavailability of Flutiform when compared with Seretide, comparing the lower strengths of two products in milder patients less likely to exacerbate meant that extrapolating the results and concluding that all patients would achieve the same efficacy response was not scientifically robust.

In summary, it was flawed to represent the limited evidence available and extrapolate FEV1 to conclude clinical comparability between Seretide and Flutiform. The aim of combination inhaled therapies was to ensure good asthma control irrespective of the product prescribed. Where, as argued, the products were sufficiently different, claims of comparability based on the use of surrogate parameters which were short-term markers of lung function were clearly inadequate, inappropriate and ill advised. To do so was disparaging and reduced confidence in the detailed evidence generated over time by the research-based pharmaceutical industry.

GlaxoSmithKline alleged that exaggerating the current available evidence to suggest that Flutiform and Seretide had clinically comparable efficacy breached Clauses 7.2, 7.3, and 7.4.

RESPONSE

Napp referred to data which it had provided to summarise the efficacy endpoints used in various studies. GlaxoSmithKline incorrectly stated that 'this [Flutiform vs Seretide] study demonstrated non inferiority of a lung function parameter (FEV1) as a primary outcome and discontinuation due to lack of efficacy as a secondary outcome'. GlaxoSmithKline failed to acknowledge that there were multiple secondary outcomes, including both lung function and patient outcomes.

Napp responded to the four arguments proposed by GlaxoSmithKline as to why the claim 'comparable clinical efficacy (P = 0.007; open label)' did not comply with the Code.

i The bioavailability of the steroid component of Flutiform had not been studied but current evidence suggested that this was likely to be lower than that for Seretide so surrogate markers of clinical efficacy were inadequate.

Napp stated that these data had not been raised by GlaxoSmithKline during inter-company dialogue. However, the bioavailability of Flutiform was discussed during the decentralised procedure regulatory submission and the conclusions of the CHMP and MHRA were publicly available in the EPAR. GlaxoSmithKline was therefore aware of the discussions and conclusions of the CHMP and the MHRA.

It was clear from the literature that pharmacokinetic data did not correlate accurately with the clinical outcomes. This position was supported by the CHMP and the MHRA. The EPAR stated that:

'Literature data indicate that even if the PK [pharmacokinetic] data accurately reflect comparative pulmonary drug deposition for Flutiform versus GSK fluticasone propionate pMDI, such differences are not of clinical relevance. Furthermore, the discordance between the PK and PD [pharmacodynamic] data for Flutiform suggests that the PK data do not accurately reflect comparative pulmonary deposition and are not a valid surrogate for clinical effect.'

The CHMP noted that the magnitude of the difference presented in the abstract by Hochhaus and Kaiser was within the normal bounds of variability for inhaled medicines.

'The CHMP noted that the differences of the magnitude observed between Flutiform and GSK fluticasone propionate in Study FLT1501 (67% relative bioavailability) are within the same range of variance as observed within patients (from inhalation to inhalation), between different batches of the same product and between different inhalers containing the same or more than one of the same active.'

In summary, the CHMP and MHRA clearly considered that the pharmacokinetic data did not reflect clinical efficacy nor provide an accurate reflection of lung deposition.

Furthermore GlaxoSmithKline fluticasone pharmacokinetic data in the UK Seretide Evohaler SPC (Section 5.2) indicated that absolute bioavailability varied between 5-11% of the nominal dose depending on the inhalation device used. These data indicated one device delivered less than half the fluticasone than another device, again supporting significant variability. Napp noted that although GlaxoSmithKline (nor the UK SPC) did not note the devices behind these figures, the data were available in the New Zealand Data Sheet for Seretide inhaler (Aerosol device). This document reported that the fluticasone propionate bioavailability for Seretide Inhaler (Aerosol) was 5.3% compared with 10.9% for fluticasone propionate monotherapy in the same device, which would suggest 51% less fluticasone delivery from Seretide than the monotherapy – more than the difference reported by Hochhaus and Kaiser (24-31%).

'The absolute bioavailability of fluticasone propionate for each of the available inhaler devices has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data. In healthy adult subjects the absolute bioavailability has been estimated for fluticasone propionate Accuhaler (7.8%), fluticasone propionate Inhaler (10.9%), Seretide Inhaler (5.3%) and Seretide Accuhaler (5.5%) respectively.' (New Zealand Data Sheet).

In conclusion, as the CHMP and MHRA noted that the difference seen was clearly within normal bounds of variability and comparable to that between Seretide and the fluticasone monotherapy suggested in the New Zealand Data Sheet, the assertion that differences in bioavailability made Napp's claim of clinical efficacy inadequate were unfounded and did not support a breach of Clauses 7.2, 7.3 or 7.4.

ii The clinical evidence presented to demonstrate comparable clinical efficacy was inadequate to substantiate this claim.

Napp did not use FEV1 alone to demonstrate clinical comparability between Seretide Evohaler and Flutiform.

As outlined above, the body of clinical evidence demonstrated that Flutiform was efficacious both in terms of lung function and patient clinical symptom domains. The findings were entirely in keeping with the expected outcome from these two widely known and well studied medicines.

Additionally the clinical data presented in the leavepieces regarding the direct head-to-head study of Flutiform pMDI vs Seretide Evohaler pMDI (Bodzenta-Lukaszyk *et al* 2011a) successfully demonstrated statistical non-inferiority for the primary endpoint of FEV1. The authors concluded that: 'Analysis of additional efficacy parameters such as other lung function tests,

patient-reported outcomes, rescue medication use, asthma exacerbations and [asthma quality of life questionnaire] AQLQ scores yielded comparable results for the two treatment groups'. This was not a study to demonstrate clinical equivalence.

The claim in question was comparable clinical efficacy and in this regard Napp referred to Case AUTH/2515/6/12, Allergan/Director v Merz in which the Panel's ruling of no breach of the Code was upheld by the Appeal Board.

'In the Appeal Board's view 'Comparable efficacy' did not imply equivalence.'

Napp also referred to Case AUTH/2357/9/10, GP v Boehringer Ingelheim:

'The Panel did not consider that comparability implied equivalence – comparable only meant that the two products were able to be compared.'

Building on the principles set out in these cases, Napp submitted that given the results of the Flutiform vs Seretide study, and given the results of the clinical package as a whole which supported these results, a claim of comparability was accurate. This evidence was acceptable to grant a marketing authorization with the therapeutic indication of:

'This fixed-dose combination of fluticasone propionate and formoterol fumarate (Flutiform inhaler) is indicated in the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting β_2 -agonist) is appropriate:

For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2 -agonist.

or

For patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 -agonist.'

This was very similar to the therapeutic indication for Seretide Evohaler:

'Seretide is indicated in the regular treatment of asthma where use of a combination product (long-acting β_2 -agonist and inhaled corticosteroid) is appropriate:

Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 -agonist

or

Patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 -agonist.'

Napp noted that the use in patients already controlled on any corticosteroid or long-acting β_2 -agonist was permitted. Clearly Flutiform had virtually the same indication as Seretide Evohaler and had an indication which would allow Flutiform

to be used in patients already adequately controlled on Seretide Evohaler.

FEV1 was a well established and accepted measure for comparing the efficacy of inhaled asthma medicines (Reddel *et al* 2009). The decision to use FEV1 as a primary endpoint was based on principles adopted from a number of CHMP guidelines as already discussed, including those referenced by Napp during inter-company dialogue, and those referenced by GlaxoSmithKline. The aim of this research was to demonstrate that Flutiform was clinically efficacious. To this end a package of clinical studies, predominantly 8-12 week studies which used FEV1 as the primary endpoint, was developed. Secondary endpoints were not powered to demonstrate non-inferiority to Seretide and yet yielded similar results between Seretide Evohaler and Flutiform. The decision that Flutiform was clinically efficacious, and the subsequent granting of the marketing authorization for Flutiform by the EMA, was based largely on studies using FEV1 as the primary endpoint.

GlaxoSmithKline alleged that the duration of the studies presented did not substantiate a claim due to no assessment of future risk as highlighted by the consensus statement by the ATS and the ERS. The predictive nature of 8-12 week FEV1 studies was extensively discussed during the regulatory process. The body of evidence for both primary and secondary endpoints generated for Flutiform, including the comparator study with Seretide, clearly demonstrated that there were clinically comparable outcomes across a range of domains. The CHMP and MHRA stated:

'In conclusion, given the long-term predictive value of FEV1, given the static nature of FEV1 after 8 to 12 weeks of treatment, and given the pattern of the FEV1 data observed in the five pivotal studies, the CHMP considers there to be no reason to anticipate that the long-term exacerbation risk with Flutiform may exceed that with fluticasone propionate alone (the "Step-up" indication) or fluticasone propionate in combination with formoterol fumarate (the "Switch" indication). These conclusions based on an indirect assessment of future exacerbation risk are consistent with and support those based on a direct observation of exacerbation rates during the clinical studies.

The CHMP was of the view that clinical data generated over 6 to 12 months to further elucidate the level of asthma control and to further assess exacerbation rates seen with Flutiform compared with fluticasone propionate administered concomitantly with formoterol fumarate or administered alone, are not required.'

Furthermore, all clinical secondary endpoints were consistent with the primary endpoint and showed comparable efficacy between Flutiform and Seretide Evohaler:

- Discontinuation due to lack of efficacy
- Change from baseline to week 12 in pre-dose FEV1
- Rescue medication use

- Mean PEF
- Asthma symptom score and sleep disturbance scores
- Asthma quality of life questionnaire scores
- Number of adverse events
- Number of exacerbations.

Both Flutiform and Seretide Evohaler were efficacious products and this formed the basis of Napp's claim. Both products had a body of data to support this. When compared in a direct head-to-head study Flutiform was found to be non-inferior, in a well recognised and accepted clinical end point. Napp submitted that this finding was supported by the secondary endpoints in the study.

Importantly these findings were supportive and in line with the other regulatory studies proving the efficacy of Flutiform. GlaxoSmithKline inferred that for products to be considered to be clinically comparable they must have the same supporting data. The claim of comparable clinical efficacy did not claim or imply clinical equivalence and was adequately supported by the available evidence. Napp stated that in view of the CHMP's conclusions and the use of appropriate end points in the Flutiform studies, 'comparable efficacy' was an entirely appropriate claim.

iii The patient selection was inadequate to allow extrapolation to all asthma severities and licensed age ranges

Studies were conducted in a sample of a population and these results were then extrapolated to the treatment population: this was a key principle of why studies were carried out. This principle was justified in this claim due to the wide body of evidence for Flutiform over a range of asthma severities and ages.

These studies included adolescents and also severe patients. The conclusion of these studies was that there was sufficient evidence to grant a 'switch licence':

'With regard to the "Switch" therapy, the CHMP accepted the discussions presented by the Applicant and was of the view that the clinical effects of Flutiform in respect of asthma control and exacerbation risk are comparable with/similar to the clinical effects of GSK fluticasone propionate and Novartis formoterol fumarate given concomitantly.

The magnitude of changes seen on a range of secondary endpoints helps to quantify the clinical relevance of the effects seen on pulmonary function and on exacerbation rate. Across a broad range of endpoints such as discontinuation due to lack of efficacy, symptom-free days and nights and the amount of rescue medication, the size of effect seen is clinically important. These findings should be taken together with the results that show that the clinical effects of Flutiform are comparable with the clinical effects of GSK fluticasone propionate and Novartis formoterol fumarate given concomitantly. This provides further support for the clinical relevance of the effects seen with Flutiform.' (EPAR section 2.2, page 8, paragraphs 2 and 3)

The Flutiform vs Seretide study was carried out in a population of mild to moderate-severe asthma patients over the age of 18, and concluded non-inferiority between the two products. The results of other studies with different age ranges (including 12 years and over) and severities (including severe), gave similar results as expected from two widely used and investigated molecules.

Specifically GlaxoSmithKline alleged that severe patients were excluded from the Seretide/ Flutiform head-to-head study. The patient selection criteria for this study included patients with a FEV1 predicted between 40-85% of normal values. Whilst Napp acknowledged that asthma severity could be determined in a number of ways, it submitted that this study included patients with severe asthma. The range of FEV1 was from 41-85% consistent with a range of asthma severity including the severe end of the spectrum. 77% of patients in this study were on an ICS/LABA so patients could be severe but well controlled on an ICS/LABA and therefore have low exacerbation risk as found in the results.

Data from these further studies did not indicate that it was invalid to extrapolate the comparability seen in clinical efficacy between Flutiform and Seretide as seen in the head-to-head study to the severe or adolescent patient groups.

Furthermore, GlaxoSmithKline alleged that the claim of comparable clinical efficacy ($p = 0.007$; open label) was unacceptable because Napp had not replicated the evidence supporting Seretide Accuhaler in the GOAL study. Napp acknowledged the robustness of the GOAL study. The GOAL study was a pivotal study that confirmed that ICS/LABA therapy provided greater asthma control than ICS monotherapy alone on both asthma control and exacerbation risk. This changed treatment practice and established ICS/LABA therapy as one of the cornerstones of asthma treatment. Napp submitted that it did not need to repeat the GOAL study for Flutiform. It had already highlighted, however, that the device used in the GOAL study was the Seretide Accuhaler, a dry powder inhaler device (DPI) and not a pMDI (see introductory section) such as Seretide Evohaler or indeed Flutiform. The GOAL study provided evidence for asthma maintenance therapy in adolescents (over age 12) but not for the entire licensed indication of Seretide, as the licence included the age 4 years and above.

However, at no stage did the leavepiece claim reference control, guideline defined control or the GOAL study.

In conclusion, Napp refuted the allegation that the patient selection was inadequate to allow extrapolation to all asthma severities and licensed age ranges. Napp maintained that severe asthmatic patients were included in both the Seretide vs Flutiform head-to-head study and in other studies of the clinical development programme leading to registration. Adolescents had also been studied, as well as limited data generated in children 4-12 years.

iv The doses studied cannot be extrapolated to infer clinical comparability of all doses

Napp referred to its response in inter-company dialogue. The following guidelines on the principle of extrapolation came from the most current CHMP guidelines (Section 4.5 CPMP/EWP/4151/00 Rev.1) on the development of orally inhaled products (OIP):

‘Dose linearity should be investigated in vitro for both the test and the reference product across all proposed strengths.

If dose linearity is demonstrated in vitro when different dose strengths of a known active substance are sought it may be sufficient to establish therapeutic equivalence clinically with only one strength of the active substance. It is usually appropriate to study the lowest strength, at more than one dose level, to enhance the sensitivity of the study.’

The in vitro linearity of the fluticasone component of Flutiform across all doses had been demonstrated and was accepted as part of the marketing authorization application. Linearity of the fluticasone component of Flutiform had been established and as with the Seretide SPC, ‘there is a linear increase in systemic exposure of fluticasone with increasing inhaled dose’ (SPC). It was therefore reasonable to infer that similar relative fluticasone bioavailability would be observed for the comparison of all strengths of Flutiform vs the corresponding strengths of Seretide.

Pharmacokinetic linearity had been demonstrated for inhaled formoterol over a (delivered) dose range of 4.5g to 36g (Derom *et al* 2007). The in vitro linearity of the formoterol component of Flutiform across dose strengths had also been demonstrated and was accepted as part of the marketing authorization application. Although to date, no study had compared the efficacy of Flutiform and Seretide Evohaler at their highest licensed doses, given the similar efficacy and tolerability profiles at the low and medium doses, and the dose linearity of the components of Flutiform, it might reasonably be inferred that, at their highest doses, both products would be likely to have comparable efficacy and safety profiles.

Furthermore the efficacy of the high dose was clearly demonstrated in the published pivotal regulatory study (FLT 3503; Bodzenta-Lukaszyk *et al* (2011b)). This study compared high strength Flutiform with high strength fluticasone monotherapy (GlaxoSmithKline fluticasone pMDI) when given concurrently with formoterol (Novartis formoterol pMDI). Considering formoterol and salmeterol had similar bronchodilatory effects over 12 hours (although as previously noted formoterol had a significantly faster onset), comparable efficacy for the high dose treatments of Seretide and Flutiform could clearly be expected. This study also confirmed superiority of Flutiform over GlaxoSmithKline fluticasone monotherapy high dose on several clinical endpoints including asthma symptom score, symptom free days, awakening-free nights, and AQLQ.

In summary, Napp maintained that Flutiform and Seretide Evohaler were clinically comparable, and it did not claim to have demonstrated clinical equivalence. Napp had presented extensive and not limited evidence for this from the total clinical development dossier, including the head-to-head study. Napp had conducted studies of appropriate duration, including moderate and severe asthma patients and adolescents, and had fully justified the use of two dose strengths. It strongly refuted the claim that its studies were ‘clearly inadequate, inappropriate and ill advised’, especially when the clinical development programme which led to a successful European registration was conceived in collaboration with the MHRA and accepted by the EMA.

For the reasons stated above Napp submitted that it had not exaggerated the current available evidence to claim clinical comparability between Flutiform and Seretide Evohaler and did not agree that it had breached Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel noted that the claim at issue ‘Comparable clinical efficacy’ was referenced to Bodzenta-Lukaszyk *et al* (2011a), a 12 week, open-label, randomised study designed to demonstrate the non-inferiority of Flutiform vs Seretide (100/500mcg or 250/50mcg twice daily) in controlling mild to moderate-severe persistent asthma in adult patients aged 18 years or over. No patients received the maximum dose of Flutiform (500/20mcg twice daily) or of Seretide (500/50mcg twice daily). The primary endpoint was non-inferiority based on mean FEV1. The secondary comparative endpoints included discontinuations due to lack of efficacy, time to onset of action, peak expiratory flow rates and other lung function parameters, amount of rescue medication use, asthma symptom scores, sleep disturbance due to asthma, daily corticosteroid doses and asthma exacerbations. The authors stated that the study demonstrated that Flutiform was comparable (non-inferior) to Seretide in terms of the primary endpoint (mean pre-dose FEV1 at week 12) and certain secondary efficacy endpoints in relation to FEV1 measurements and discontinuation due to lack of efficacy. Flutiform was superior to Seretide in terms of time to onset of action. The authors stated that analysis of additional efficacy parameters yielded ‘similar results’ (lung function tests, patient reported outcomes, rescue medication use, asthma exacerbations and AQLQ scores).

Whilst noting that FEV1 was a fundamental efficacy measurement, the Panel considered the broad unqualified claim ‘comparable efficacy’ implied more than a measurement of FEV1. In this regard the Panel noted that the secondary outcome data in Bodzenta-Lukaszyk *et al* (2011a) showed that Flutiform and Seretide were similar in a number of additional relevant efficacy measurements.

The Panel noted GlaxoSmithKline’s submission that as evidenced by the low exacerbation rates, severe asthmatics were not included. The Panel also noted Napp’s contrary comments and its submission that as 77% of patients were on a combination product severe asthmatics could be well-controlled and thus have

a low exacerbation risk. This was inconsistent with Napp's subsequent assertion that there was no further data to indicate that it was invalid to extrapolate the results of Bodzenta-Lukaszyk *et al* (2011a) to severe or adolescent asthmatics. Bodzenta-Lukaszyk *et al* (2011a) described the patient population as 'mild-to-moderate - severe, persistent asthmatics' which the Panel considered might be read as including patients who had asthma which was anything from mild- to moderately-severe. To be included in the study patients were required to demonstrate an FEV1 of $\geq 40\%$ and $\leq 85\%$ of predicted normal values. The Panel noted that Mansur and Kaiser (2012) defined eligible patients with mild-to-moderate - severe asthma as those with an FEV1 of between 40-85% of predicted normal values. The Panel also noted that the ATS/ERS 2009 joint statement stated that asthma severity was defined as the difficulty of controlling asthma with treatment. Severity largely reflected the required level of treatment and the underlying disease state during treatment.

The Panel noted that Section 4.2 of the Flutiform SPC stated 'Flutiform inhaler in any strength is not recommended for use in children less than 12 years of age; Flutiform inhaler should not be used in this young age group'. In addition, it was stated that Flutiform 250/10mcg inhaler 'should not be used in adolescents'. The Panel noted that according to its SPC, Seretide 25/50mcg could be prescribed from the age of 4 years. There was no data available for use of Seretide in children aged under 4 years. From the age of 12 years children could be treated with all three doses of Seretide (25/50mcg, 25/125mcg and 25/250mcg).

The Panel noted that the heading to the page at issue in leavepiece 1 read 'Why should I prescribe Flutiform instead of Seretide Evohaler?' The subheading read 'Prescribe flutiform instead of Seretide Evohaler because it can deliver:'. The facing page detailed the high, medium and low doses of Flutiform. The Panel considered that many readers would already be familiar with the Seretide Evohaler which the Panel noted was first granted a market authorization in 2000. The Panel considered that the broad, unqualified claim 'Comparable clinical efficacy (P = 0.007, open label)' implied that Flutiform could be used in all of those patients for whom Seretide might be prescribed and that there was robust comparative clinical data in relation to all doses and patient populations and that was not so. The Panel noted that there was some comparative efficacy data but considered that insufficient information about the study had been provided to enable the reader to accurately interpret the claim which was consequently misleading and incapable of substantiation. The Panel noted that the first page of the detail aid stated that Flutiform was '[fluticasone/formoterol] combined for the first time for asthma maintenance therapy for patients 12 years and older (low and medium strengths); adults (all strengths)'. However, this statement was in a small font size such that, in the Panel's view, it would be missed by many readers. The Panel did not consider that the statement was prominent enough to set the rest of the leavepiece in context. In the Panel's view the statement on the first page did not negate the otherwise misleading impression given by the claim on page 2 of 'Comparable clinical efficacy'. A breach of Clauses 7.2, 7.3, and 7.4 was ruled.

The Panel noted that leavepiece 2 was different. A preceding bullet point explained that Flutiform 50/5mcg and 125/5mcg were licensed for use in patients aged 12 years and above. The immediate subheading to the claim in question made it clear that patients had mild to moderate-severe persistent asthma. However, it had not been made clear that only medium and low doses of Seretide Evohaler had been compared in patients aged 18 years or over. The Panel also noted its comments above about the secondary clinical endpoints in Bodzenta-Lukaszyk *et al* (2011a). On balance, the Panel considered that the rulings made in relation to leavepiece 1 also applied to leavepiece 2. The claim 'Flutiform had comparable clinical efficacy to Seretide Evohaler (P= 0.007; open label)' was not sufficiently qualified and was therefore misleading and incapable of substantiation; a breach of Clauses 7.2, 7.3 and 7.4 was ruled.

2 Claim 'The efficacy and tolerability of flutiform were sustained for up to 12 months'

The claim at issue appeared in leavepiece 2 directly beneath the claim at issue at Point 1 above 'Clinical trial data have shown that in patients with mild to moderate-severe persistent asthma: flutiform had comparable clinical efficacy to Seretide Evohaler (P = 0.007; open label)'. The claim was referenced to Mansur (2008).

The claim was referenced to Mansur (2008).

COMPLAINT

GlaxoSmithKline stated that Mansur (2008) was a 12 month, open label, safety study, with no comparator arm. The abstract was recently published as a full paper (Mansur and Kaiser 2012) wherein the full dataset was disclosed.

The publication did not support the claim 'The efficacy and tolerability of flutiform were sustained for up to 12 months'. GlaxoSmithKline alleged that the claim exaggerated the results as the study was a 12 month, open label, safety study, with no comparator arm. Also, the claim did not provide the reader with enough information to make an accurate assessment of the current evidence.

Mansur and Kaiser measured FEV1 as a secondary endpoint in a 12 month safety study utilising no comparator arm over the 12 months. The term 'efficacy' was broad, and did not relate to the actual evidence which only demonstrated spirometric secondary endpoints and did not demonstrate any clinical efficacy endpoints.

The claim 'The tolerability and efficacy of flutiform were sustained for up to 12 months' also appeared directly below the claim '... comparable clinical efficacy to Seretide Evohaler ...'. GlaxoSmithKline alleged that the juxtaposition of these two claims misled the reader into believing 'comparable clinical efficacy' had been demonstrated over 12 months.

During inter-company dialogue Napp proposed a revision to read: 'The tolerability and efficacy of Flutiform were sustained for up to 12 months (open label spirometric secondary endpoints $p < 0.001$)'.

GlaxoSmithKline acknowledged that the two claims referred to different references; however, it was not clear that the claims related to two separate studies. Readers might assume that the second study was an extension of the first.

GlaxoSmithKline noted that Napp disagreed with its request that in addition to the revision proposed above, Napp also include the phrase 'no comparator' within the body of the text. In GlaxoSmithKline's view this would ensure that when the two claims were juxtaposed, it would be clear to the reader that the two trials were indeed different and that this was not an extension of the head-to-head study. Napp declined and stated that the provision of a reference was adequate. GlaxoSmithKline did not agree that the provision of different references was justification for not making the facts clear to the reader.

GlaxoSmithKline alleged that the juxtaposition of the two claims in both the current and proposed revised wording was misleading in breach of Clause 7.3.

RESPONSE

Napp submitted that the two parts of the claim (ie efficacy and tolerability), were substantiated, firstly by the Mansur abstract, 'Longterm safety study of FlutiForm HFA in asthma', and secondly by the full paper by Mansur and Kaiser, 'Long-term Safety and Efficacy of Fluticasone/Formoterol Combination Therapy in Asthma'. In the full paper, the efficacy variables, measured as secondary endpoints, were defined as spirometric measures with qualification of efficacy defined as significant improvements in measures of change, which included FEV1 and change in peak expiratory flow rate (PEFR) (l/min), specifically of:

- a) mean change from pre-dose at baseline to pre-dose assessments at each visit and last visit, and
- b) mean change from pre-dose at baseline to 1 hour post-dose at weeks 2 and 4 and at months 2 and 3.

Other measures of efficacy included FEV1 % predicted, forced vital capacity (FVC), asthma symptom scores and sleep disturbance scores.

Mansur and Kaiser demonstrated that the mean change at each patient visit was highly significant for all the spirometric efficacy parameters that were measured, and of particular note, the mean change in FEV1 and change in PEFR (l/min). These included the patient visits at months 3, 6 and 12.

Napp submitted that Mansur and Kaiser clearly defined the measures of efficacy, that they disclosed the full data set, the claim, 'The efficacy and tolerability of flutiform were sustained for up to 12 months', was substantiated and therefore provided the reader with enough information and guidance to make an accurate and balanced assessment of current, and other available evidence.

With regard to tolerability Napp submitted that Mansur and Kaiser, a 6-12 month open label safety study with patients aged 12 years and older, which included 466 patients in the full analysis set and 390 in the

per protocol set, demonstrated that the incidence of adverse events, and also adverse event profile, [174 patients (36.9%), with the majority of adverse events either mild or moderate in severity] was in line and not unusual with that observed in previous long-term (1 year) studies of ICS/LABA combinations. For example, by comparison, after 1 year's treatment in adults with persistent asthma, the overall incidence of adverse events with fluticasone propionate/salmeterol xinafoate (250/50mcg twice daily) and budesonide/formoterol fumarate (200/6µg once daily or 200/6 - 400/12µg twice daily) was 48.6% and 52.3% respectively. Thus, the rates of adverse events reported by Mansur and Kaiser (36.9%) did not appear to be unusual for combination therapy administered for up to 1 year.

Mansur and Kaiser also reported that there were no significant or abnormal trends in clinical assessments and vital signs demonstrated over the 6-12 month period, that no deaths were reported, and that the 12 serious adverse events experienced by the 10 (2.12%) patients were considered not to be related or unlikely to be related to the study medicine. Therefore, Napp submitted that the claim at issue was substantiated.

Napp noted GlaxoSmithKline's allegation that the juxtaposition of the claim, placed below a separate claim of 'flutiform had comparable clinical efficacy to Seretide Evohaler (P = 0.007; open label)' misled readers as they would assume that this second study was an extension or subset of the first which it was clearly not. Napp submitted that it was clear that the two claims were placed under a title of 'Clinical trial data ...' which was meant in the plural and referred to separate independent data sets. Furthermore, the two independent claims were clearly and individually referenced and placed on separate lines; this reinforced their mutually exclusivity and independence. If Mansur and Kaiser had been derived from the same efficacy trial data as for the head-to head Seretide/Flutiform study it would be usual to indicate this with the same numbered reference. Lastly, there was no paragraph or sentence indentation of the second claim, which further supported the mutually exclusive individuality of these two claims – the second claim was clearly shown not to be part of a 'follow-on study' from the first.

In inter-company dialogue, GlaxoSmithKline disagreed that the provision of different references provided in small italics were justification for not making this clearer to the reader. In response Napp had noted that 'The different references are not in small italic on the leavepiece. They are superscript, are based on Vancouver style (www.icmje.org) and are at least 2mm in height (exceeding Clause 4.1 supplementary information for legibility – where a lower case letter 'x' is no less than 1 mm in height). Napp maintain that having two different reference numbers clearly do not imply that the two statements are from the same study.'

After inter-company dialogue, for the purposes of constructive progress and pragmatic resolution, Napp proposed to reword the claim for further clarification to: 'The tolerability and efficacy of flutiform were sustained for up to 12 months (open label spirometric secondary endpoints P<0.001)'. GlaxoSmithKline did

not accept this, and asked for additional wording to the claim that 'In a separate study the tolerability of ...'. Napp did not accept this for the reasons stated.

In conclusion, Napp submitted that the juxtaposition of the two claims in the leavepiece at issue followed the well accepted medical/scientific writing principles by being clearly independently and sequentially referenced. They were not misleading and not in breach of Clause 7.3.

PANEL RULING

The Panel noted GlaxoSmithKline had raised a number of allegations about the claim in question. During inter-company dialogue Napp had agreed to amend the claim. It appeared that the remaining unresolved issue was the allegation that a misleading impression was given by the juxtaposing of the claim in question to that considered at Point 1 above. This was the sole issue considered by the Panel.

The Panel noted that Mansur and Kaiser was an open label study in which mild to moderate-severe asthmatics age 12 years and over were treated twice daily with low or medium dose Flutiform for 6 months (n=256) or 12 months (n=216). The primary and secondary objectives were the long-term safety and efficacy of Flutiform. The study demonstrated statistically significant improvements overall and for both treatment groups for each efficacy assessment. Flutiform demonstrated a good safety and efficacy profile over the 12 month study period.

The Panel noted that the claim at issue 'The efficacy and tolerability of Flutiform were sustained for up to 12 months' appeared immediately beneath that at issue at Point 1 above, 'Flutiform had comparable clinical efficacy to Seretide Evohaler (P= 0.007, open label)'. The Panel considered that the juxtaposing of the claims was such that the claim at issue would inevitably be read in light of that preceding it and thus readers would infer that comparable clinical efficacy with Seretide Evohaler was demonstrated for up to 12 months and that was not so. The claim in question was misleading on this point as alleged and a breach of Clause 7.3 was ruled.

3 Question 'Why should I prescribe flutiform instead of Seretide Evohaler?'

This question appeared in leavepiece 1 as the heading to page 2; it was presented as a search in a web browser. The question was followed by 'Prescribe flutiform instead of Seretide Evohaler because it can deliver:' which was followed by four bullet points.

COMPLAINT

GlaxoSmithKline alleged that Flutiform was presented as a direct substitute to Seretide Evohaler but it was not a suitable substitute for all patients who were eligible for Seretide. There were several clinically important differences that were not mentioned in the leavepiece. The only difference between the two products highlighted in the leavepiece was that Flutiform had a faster onset of action, although no clinical rationale was provided to support why, in maintenance therapy, a faster onset of action was

relevant. The claim for a faster onset of action claim was addressed in Point 5 below.

Seretide Evohaler and Flutiform differed in three important and clinically relevant aspects. Firstly, Seretide 50 Evohaler was licensed from 4 years and older whilst Seretide 125 and 250 Evohalers were licensed from age 12 years and older. Flutiform 50 and 125 were licensed from 12 years and older and Flutiform 250 was licensed from age 18 years and older. Secondly, unlike Seretide, Flutiform contained ethanol and so it was an unsuitable treatment for certain ethnic groups and thirdly, Flutiform was licensed for use with the AeroChamber Plus spacer device only. Seretide was licensed for use with both the Volumatic and AeroChamber Plus spacer devices.

GlaxoSmithKline alleged that the omission of clinically important marketing authorization differences when advising that Flutiform was an alternative treatment option to Seretide Evohaler misled prescribers. The information presented was not fair, balanced or objective and created confusion between the two products. As presented, it was selective and insufficiently complete and so the recipient could not determine an accurate or comprehensive view of the therapeutic relevance and value of the medicine. The omission of key information detailing the licensed differences meant that prescribers were not informed that Flutiform was unsuitable for some patients prescribed Seretide. GlaxoSmithKline alleged that this approach might encourage off-label prescribing and usage that compromised safety and put patients at risk in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Napp submitted that the full licensed indication for Flutiform was stated on the front page of the leavepiece and before any mention of Seretide. In addition, the licensed age ranges for Flutiform were stated twice on the front page of the leavepiece. There was, therefore, no confusion about the group of patients to which this whole leavepiece was relevant. Readers would only consider prescribing in this patient group and Napp therefore refuted the allegation that the claims were misleading; patient safety was not in doubt.

Napp noted that the therapeutic indications of the two products were almost identical and so in that regard it was entirely reasonable to present therapeutic options, within the licensed indication.

In response to the comment that clinically important differences between the marketing authorizations for Flutiform and Seretide Evohaler misled the prescriber, Napp maintained its position that the leavepiece did not suggest that all existing patients might be switched to Flutiform. Moreover, the leavepiece did not specifically advocate that existing Seretide Evohaler patients be switched and could include new asthma patients not adequately controlled (in accordance with the licensed indications).

Many factors that influenced prescribing decisions. Napp noted GlaxoSmithKline's submission that the inclusion of ethanol as an excipient was an important

influencing factor for prescribing but disputed that the presence of such small amounts of it were a significant consideration in general prescribing. The ethanol content was negligible, it was within the mg range and below that which was a cause for concern (alcohol content below 100mg per dose was considered negligible by the EMA). To put this into context alcohol could be present naturally in small amounts in many foodstuffs particularly in ripened fruit and fresh (unpasteurised) fruit juice.

With regard to the ethanol content, Napp was uncertain about the specific ethnic groups to which GlaxoSmithKline had referred; many alcohol-containing asthma therapies were approved in countries with predominantly Muslim populations eg Fostair (Pakistan and Turkey) and Salamol (UAE). Those religions that prohibited the consumption of alcohol might tolerate the small amounts of alcohol used in medicines. Furthermore, many other pMDIs used in routine practice, for the treatment of asthma, contained small amounts of alcohol as an excipient, something which many doctors would know. For those rare situations where ethanol needed to be considered the information was available in the prescribing information and in the patient information leaflet (PIL). To illustrate the principle it was not a requirement or common practice to include specific mention of lactose as an excipient even though this made a medicine unsuitable for certain groups of patients, eg those allergic to lactose. Seretide Accuhaler (DPI) contained lactose as an excipient but it did not know of any GlaxoSmithKline marketing materials which explained this. Both Napp and GlaxoSmithKline patient information leaflets noted the alcohol and lactose excipients respectively.

Page 3 of the leavepiece stated that Flutiform was 'Licensed for use with an AeroChamber Plus Spacer', the prescribing information also clearly stated that 'the AeroChamber Plus spacer device is recommended in patients who find it difficult to use inhalers'. Therefore, when making a clinical decision, the fact that Flutiform was only recommended for use with the AeroChamber Plus was made clear. If the clinician wished to use a spacer, that option was available with the AeroChamber Plus, so the prescriber could use the information provided to make an informed decision about the most appropriate product for their patient.

Napp submitted that it had not omitted key information and denied breaches of Clauses 7.2, 7.3, or 7.4.

PANEL RULING

The Panel noted that both the heading and subheading to page 2 referred to prescribing Flutiform 'instead of Seretide Evohaler'. The subsequent bullet points explained why, in Napp's view, Flutiform should be so prescribed. No information was given about when such a substitution would be appropriate. The Panel noted that Flutiform was not a suitable substitute for patients aged between 4 and 11 years who could be treated with Seretide Evohaler. The Panel noted its comment above at Point 1 that many readers would

already be familiar with Seretide Evohaler. The Panel considered that in the absence of information to the contrary, readers would assume that Flutiform could be substituted for Seretide Evohaler in all circumstances and that was not so. The information about Flutiform's licensed indication in relatively small print on page 1 was insufficient to negate the unequivocal impression given by page 2. The Panel considered that page 2 was misleading and incapable of substantiation on this point. A breach of Clauses 7.2, 7.3 and 7.4 was ruled.

4 Claim 'Faster onset of action (P<0.001; secondary endpoint)'

This claim appeared on page 2 of leavepiece 1 immediately beneath the bullet point at issue at Point 1 above, 'Comparable clinical efficacy'. The claim was referenced to Bodzenta-Lukaszyk (2011a).

COMPLAINT

GlaxoSmithKline stated that 'Faster onset of action' was presented in both leavepieces as the key differentiator between Flutiform and Seretide Evohaler. The actual times to onset of action were not stated in the published paper, and importantly, it had not been established that a shorter time to onset of action was of value in a controller medicine. Furthermore, Napp did not provide any clinical evidence to substantiate the clinical relevance of this claim.

With regard to the clinical relevance of the claim, in inter-company dialogue Napp had hypothesised that 'Faster onset of action' might lead to improved patient preference and so improved adherence. However, the trend seen in the only head-to-head study Bodzenta-Lukaszyk *et al* (2011a) indicated that the onset of action difference became less apparent as time progressed, thus any purely theoretical benefit would presumably manifest in the early stage of therapy. This was, however, not substantiable as the evidence actually contradicted such a hypothesis. The data showed that patients significantly favoured Seretide (Odds ratio 0.495 CI 0.289, 0.848) over Flutiform with no significant difference presented in adherence rates to study medication. Napp's own data thus negated such a hypothesis.

GlaxoSmithKline stated that in leavepiece 1 the claim 'Faster onset of action' appeared on the same page and next to the bold claim 'flutiform is licensed for maintenance therapy and not for acute symptom relief'.

A claim for a faster onset of action was typically synonymous with a reliever (or SMART [Symbicort Maintenance and Reliever Therapy]) therapy and could, potentially, lead to inappropriate off-label use of Flutiform inconsistent with its SPC and pose risks to patient safety.

GlaxoSmithKline maintained that Napp had failed to substantiate the clinical relevance of this claim and the audience was not given appropriate information on which to assess the clinical relevance or impact of a faster onset of action in maintenance therapy with this controller medication. The juxtaposition

of claims in leavepiece 1 misled the reader and potentially encouraged Flutiform to be misused and prescribed off-licence. GlaxoSmithKline alleged that the claim was in breach of Clauses 3, 7.2 and 7.4.

RESPONSE

Napp submitted that the time to onset of action for formoterol was included in Section 5.1 of the Flutiform SPC, which stated that 'The onset of bronchodilating effect is rapid, within 1 - 3 minutes'.

Napp submitted that its accurate and objective data with regard to onset of action presented in leavepiece 1 was:

'Prescribe flutiform instead of Seretide Evohaler because it can deliver:

- Comparable clinical efficacy (P = 0.007; open label)
 - o Faster onset of action (P<0.001; secondary endpoint)

The leavepiece stated a fact, substantiated by the results of a clinical trial that Flutiform had a faster onset of action (P<0.001; secondary endpoint) compared with Seretide (Bodzenta-Lukaszyk *et al* (2011a)). GlaxoSmithKline acknowledged this point during inter-company dialogue.

With regard to GlaxoSmithKline's specific concerns, Napp proposed during inter-company dialogue that the claim was included as the speed of onset of a LABA was an area of emerging clinical opinion as per Clause 7.2. Napp submitted that as discussed in inter-company dialogue, it was relevant to highlight the differences in onset of action between Flutiform and Seretide Evohaler as it was a key differentiator between LABAs and of clinical relevance for asthma maintenance therapy. GlaxoSmithKline would know from its own clinical development programme for fluticasone furoate/vilanterol that the speed of onset of a LABA was a clinically relevant measure.

The difference in time to onset of action between formoterol and salmeterol was frequently identified and referred to in the literature. Palmqvist *et al* (1999) stated:

'... Important pharmacological differences between these drugs have been documented in vitro and in patients. First, formoterol has a faster onset of action compared with salmeterol, which has been documented both in airway smooth muscle preparations as well as in asthmatic patients.'

Napp submitted that other articles focussed almost entirely on this difference between formoterol and salmeterol (van Noord *et al* 1996 and Grembaile *et al* 2002). It was therefore, clearly a clinically interesting difference between the two combinations.

Napp noted that GlaxoSmithKline's clinical studies of fluticasone furoate/vilanterol vs fluticasone propionate/salmeterol and vilanterol vs salmeterol used onset of action as an endpoint, as determined by a 12% improvement (considered to be a minimal clinical difference (Santanello *et al* 1999), or 200ml improvement on day 0 and day 84 (clinicaltrials.

gov). The fact that this was included within current GlaxoSmithKline clinical trials highlighted the fact that this was a clinically relevant measure. Napp further noted that Cazzola *et al* (2011) identified onset of action as an important criteria for creating any new LABA and this, coupled with the above studies, reinforced that rapid onset of action was a clinically relevant differentiator.

Napp submitted that diurnal rhythm dictated that pulmonary function was poorest in the early mornings and this natural diurnal variation was often exaggerated in patients with asthma (Hetzel and Clark 1980, Hetzel 1981 and Clark 1987). Rapid bronchodilation following the morning dose of maintenance medication might therefore benefit these patients. This was of clinical relevance to the reader of the leavepiece.

To highlight the importance of time to onset of action in maintenance therapy, the following references which were presented to GlaxoSmithKline in inter-company dialogue:

Bender *et al* (2007) described the results from a survey of adult patients with asthma about the factors which influenced their decisions about when to use their asthma controller medications. Adherent and non-adherent patients were asked about factors they perceived to be important for maintenance therapy. Many patients, and particularly the non-adherent patients, expressed a strong preference for medications that worked quickly.

Harding *et al* (2009) determined whether patient perceptions about onset of action were clinically meaningful. It was concluded that showing that patients could feel a maintenance inhaler therapy work right away was meaningful to clinical decision-making, and the attribute could potentially improve patient adherence with therapy.

Murphy and Bender (2009) reviewed patient perspectives and preferences for controller medications and discussed the importance of speed of onset of action for various treatment regimes. The review further supported the premise that onset of action was an area of emerging clinical and/or scientific opinion.

Leidy *et al* (2009) stated that 'Feeling a maintenance therapy work right away may provide positive reinforcement and may offer one way to improve adherence in patients with asthma'. The authors further stated: 'Most patients reported that feeling their medication work right away is reassuring and would help them manage their asthma'.

Leidy *et al* (2008) outlined the process of developing a test to assess patient perception and satisfaction with feeling an asthma medication working right away. The authors stated 'A maintenance medication that patients with asthma can feel working shortly after administration could reinforce daily treatment and improve satisfaction, adherence, and outcomes'.

Hauber *et al* (2009) quantified the relative importance that patients who used combined ICS/LABA

maintenance medication placed on onset of action. The authors concluded 'Patients with asthma have clear preferences for perceived onset of effect in maintenance medications ... may increase the use of and adherence to maintenance medications'.

Napp further referred to the following peer-reviewed articles from its own studies that further supported for the importance of onset of action.

Thomas *et al* (2011) discussed physicians' attitudes towards the effectiveness of different single- or dual-inhaler combinations of an ICS and a LABA in the context of asthma management, including reasons for their choice. The most common reason for selecting a given combination was rapid onset of action (60%) followed by high potency of the steroid (39%).

Bousquet *et al* (2012) reported on a Delphi process to determine attributes perceived to be important in the selection of combination therapy followed by a pan-European survey to assess the attitudes, perceptions and prescribing behaviour of a larger population of physicians with a specialist interest in asthma treatment. Both the Delphi process stage and the pan-European survey showed that onset of action was one of the most important aspects for an ICS/LABA combination.

Napp noted that GlaxoSmithKline had also raised concerns that the onset of action difference became less apparent as the study progressed, thus any purely theoretical benefit would presumably manifest in the early stages of therapy. Napp had addressed this in inter-company dialogue. The fact that the size of the difference reduced over the course of the study was entirely expected as control improved, leaving less room for improvement. The telling point was the fact that the faster onset could still be demonstrated, even after three months of maintenance therapy once near-maximal improvements in FEV1 had been reached.

Napp had further characterised the faster onset of action seen both at the beginning of the head-to-head study, and after 12 weeks in post hoc analysis. Aalbers *et al* (2012) confirmed and expanded on the results from the head-to head study, Bodzenta-Lukaszyk *et al* (2011a), highlighting that Flutiform had a faster onset of action at all study visits.

Interestingly, assessment of patient perceptions of onset of action also showed that patients could perceive a difference between combinations containing either formoterol or salmeterol (O'Conner *et al* 2010).

Napp submitted that the suggestion that the results of a patient assessment of medication endpoint negated any other hypothesis was clearly not valid. The endpoint was exploratory and came from a non-validated question and was not sourced from any established questionnaire; it captured the response to the question 'How was the study medication at treating your asthma?' and had a five-point scale for response. Data were captured at end of study and would reflect overall experience with medication and not the benefit of a rapid bronchodilation.

To assess the benefit to patients of a faster bronchodilation would require more specific validated questionnaires such as the 5-item Onset of Effect Questionnaire (OEQ) which was not included in this study (Hauber *et al* 2009).

Napp also noted that in the context of a clinical trial the patient assessment of medication was 'very good' or 'good' for 84% of patients treated with Flutiform and 91% treated with Seretide at Day 84. Both treatments were therefore rated highly, and only 1% in each group scored either device as 'very poor'. However, this might not be reflected in the real world setting where patients were not frequently reviewed by a health professional. The link that GlaxoSmithKline had tried to make between two different endpoints, namely speed of onset of action and patient satisfaction, was still not clear, and did not negate this response and that provided during inter-company dialogue.

For these reasons, Napp submitted that the claim was substantiated. Onset of action was of clinical interest for a maintenance therapy, and therefore a relevant point to mention. Napp denied breaches of Clauses 7.2 and 7.4.

Napp submitted that the juxtaposition of the claims 'Faster onset of action' and 'flutiform is licensed for maintenance therapy and not for acute symptom relief' was appropriate and deliberate to clearly highlight that Flutiform was licensed for maintenance therapy and not for acute symptom relief despite its relatively fast onset of action. Napp considered it necessary to include such text to ensure that prescribers were clear that although Flutiform included formoterol (the same LABA included in Symbicort and Fostair which could both be used as maintenance and reliever therapy) it was only licensed for use in maintenance therapy and that any use for acute symptom relief would be off-licence. Napp therefore denied a breach of Clause 3 as it had clearly indicated in large font that Flutiform was licensed for maintenance therapy and not for acute symptom relief.

Napp submitted that it had substantiated the clinical relevance of the claim and provided appropriate information as part of the inter-company dialogue. The juxtaposition did not mislead the reader and so did not encourage off-licence use of Flutiform. Napp denied a breach of Clauses 3, 7.2 and 7.4.

PANEL RULING

The Panel noted GlaxoSmithKline's submission that the claim 'Faster onset of action' appeared in both leavepieces. It did not appear in leavepiece 2 and thus the Panel made no ruling in relation to that leavepiece.

The Panel noted both parties' submissions about the clinical relevance of the claim. In particular, the Panel noted the studies submitted by Napp indicated overall that onset of action was of clinical interest and relevance for a maintenance therapy. The claim was not misleading or incapable of substantiation on this point. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that alongside the bullet points, including that at issue above, was an image of a Flutiform pMDI beneath which and in the bottom left-hand corner of the page, was the prominent claim 'flutiform is licensed for maintenance therapy and not for acute symptom relief'. The Panel did not consider that the juxtaposing of the claim 'Faster onset of action' and the description of its licensed use for maintenance therapy misled the reader as alleged or promoted it in a manner that was inconsistent with its marketing authorization. The page made it clear that Flutiform was licensed for maintenance therapy. The Panel further noted that the claim was within the context of 'Why should I prescribe flutiform instead of Seretide Evohaler?'. The Panel considered that prescribers would be familiar with Seretide and know that it was only indicated as a maintenance therapy. No breach of Clauses 3.2 and 7.2 was ruled.

During its consideration of this matter the Panel noted that leavepiece 2 featured the closely similar claim 'The same inhaled steroid combined with a faster-acting LABA' referenced to Bodzenta-Lukaszyk (2011a). Although this particular claim was not cited by GlaxoSmithKline the Panel queried whether it would be caught by the ruling on this point and requested that Napp be advised of its concern in this regard.

5 Cost-effectiveness claims

The fourth bullet point on page 2 of leavepiece 1 beneath the heading 'Prescribe flutiform instead of Seretide Evohaler because it can deliver:' read 'Improved cost-effectiveness'. Page 3 featured a table which compared the acquisition costs of Flutiform and Seretide Evohaler.

Leavepiece 2 was headed 'Flutiform (fluticasone propionate/formoterol fumarate) inhaler as a cost-effective treatment for asthma management' and discussed the economic burden of asthma and the recommendation from the National Institute for Health and Care Excellence (NICE) to prescribe the least costly combination device with Seretide Evohaler accounting for 43% of these inhalers. A subsequent section headed 'Rationale for flutiform' claimed that 'flutiform provides the clinician with a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Steps 3 or 4 of the SIGN/BTS guidelines'. A chart of potential annual acquisition cost savings followed within a separate section.

The claims for 'cost-effective' or delivering 'Improved cost-effectiveness' were referenced to 'Data on file. – Flutiform cost-effectiveness analysis'.

COMPLAINT

GlaxoSmithKline noted that the supplementary information to Clause 7 stated:

'The economic evaluation of medicines is a relatively new science. Care must be taken that any claim involving the economic evaluation of a medicine is borne out by the data available and does not exaggerate its significance. To be acceptable as

the basis of promotional claims, the assumptions made in an economic evaluation must be clinically appropriate and consistent with the marketing authorization.'

GlaxoSmithKline stated that the data cited in support of the claims at issue most closely resembled a cost-minimisation analysis which of itself required robust evidence for clinical equivalence with respect to patient outcomes. In this instance, the cost-minimisation analysis assumed that the health benefits of Seretide and Flutiform were 'similar' and then dismissed efficacy, and the resultant analysis focussed entirely on costs.

GlaxoSmithKline stated that there was no randomised, double-blind, head-to-head study which compared Seretide Evohaler and Flutiform. The only comparison between the two was a 12 week, open label, non-inferiority study investigating the low and medium doses in adults using a spacer device (Bodzenta-Lukaszyk *et al* 2011a). As highlighted earlier, the primary endpoint of the trial was non-inferiority of FEV1. High doses of Seretide and Flutiform had not been compared and studies of high dose were an essential prerequisite to establish comparable safety with any degree of certainty.

The clinical efficacy proven with Seretide had demonstrated guideline-defined control (which included the following asthma outcomes: PEF, rescue medication use, symptoms, night-time awakenings, exacerbations emergency visits, and adverse events) over a 12 month period in the GOAL study. Therefore, the assumption of comparable clinical efficacy for the basis of the cost-minimisation analysis could not be justified.

Furthermore, there were a number of issues with the methodology and assumptions used within the analysis. These had been highlighted by GlaxoSmithKline in inter-company dialogue but not addressed by Napp. A summary was provided below:

- Fostair was included in the cost-minimisation analysis, however, no mention of how clinical equivalence with Fostair was established prior to the subsequent cost analysis. There were no head-to-head clinical trials comparing Flutiform and Fostair.
- Fostair could also be used at a dose of 1 puff twice daily and cost less than Flutiform at the lowest dosing level. In addition Seretide 500 Accuhaler cost less at the highest dosing level. Both of these pertinent clinical possibilities had been excluded from the analysis.
- There were some patients who could not be switched to Flutiform or who would require additional consultation and prescription costs who had not been accounted for in the analysis (eg patients who used a Volumatic Spacer or who were unable to use inhalers containing ethanol)
- Consultation costs or the consequences of worsening asthma control in the absence of a consultation were not incorporated within the analysis or within the potential savings within the leavepiece itself.

GlaxoSmithKline alleged that the above claims were not fair, accurate or balanced. The cost comparisons made were misleading and not substantiated by the cited reference. Breaches of Clauses 7.2, 7.3 and 7.4 were alleged.

RESPONSE

Napp submitted that in order to determine whether a medicine was cost-effective, several forms of economic evaluation could be undertaken. The main difference between the different types of evaluations was in how the benefits were measured and valued as stated by Drummond *et al* (1997):

Cost-effectiveness analysis – ‘... analyses, in which costs are related to a single, common effect’

Cost-benefit analysis – ‘Analyses that measure both the costs and consequences of alternatives in monetary units’

Cost-utility analysis – ‘Analyses that employ utilities as a measure of the value of programme effects’

Cost-minimisation analysis – ‘Where the consequences of two or more treatments or programmes are broadly equivalent, so the difference between them reduces to a comparison of cost’.

Napp maintained that Flutiform had demonstrated ‘comparable clinical efficacy’ to Seretide Evohaler and was ‘broadly equivalent’ and so a cost-minimisation analysis was an appropriate form of economic evaluation. Only medicine costs were compared and the cheapest intervention would provide the best value for money and was therefore deemed to be a cost-effective treatment option. Given Flutiform had lower costs than Seretide Evohaler, it was a cost-effective treatment option.

In generating the model, the results of non-inferiority trials were accepted as the basis for cost-minimisation analyses, as stated by Haycox and Walker (2009).

‘... with many cost-minimisation analyses being based on trials that were not specifically designed to prove clinical equivalence. Many sources of clinical evidence can be used to support economic evaluations; however the “gold standard” is normally considered to be the RCT [Randomised Control Trial]. Such trials can be subdivided into superiority trials, equivalence trials and, as has been done more recently non-inferiority trials.’

Additionally, Flutiform was evaluated by the Scottish Medicines Consortium (SMC) following an abbreviated submission. Based on the evidence submitted, the SMC accepted Flutiform for use and stated:

‘[Flutiform] has demonstrated clinical non-inferiority to another combination product containing a corticosteroid and long-acting 2-agonist and may offer cost savings.’

The SMC accepted Flutiform for use based on the study in question and a cost-minimisation model and Napp submitted that this supported the cost-effectiveness statements. Reviews had also been published by PrescQIPP (December 2012) and the Midlands Therapeutics Review & Advisory Committee (September 2012) in support of Flutiform cost-effectiveness.

Napp disagreed with GlaxoSmithKline’s statement that cost-minimisation analysis could only be used when there was ‘robust evidence of clinical equivalence’. The head-to-head study of Flutiform and Seretide Evohaler was a randomised, controlled, non-inferiority trial (Bodzenta-Lukaszyk *et al* 2011a). Napp noted that GlaxoSmithKline had again referred to the proven clinical efficacy of Seretide in the GOAL trial, without clearly explaining that this trial was for Seretide (DPI) Accuhaler and not the Evohaler.

The Napp data on file was cited to substantiate the claims in the leavepieces and as there were no comparisons with Fostair or Seretide Accuhaler within the materials, Napp was not clear how relevant GlaxoSmithKline’s comments were on this. However, to answer the specific points raised Napp referred to the following:

i. Fostair was included in the cost-minimisation analysis, however, no mention of how clinical equivalence with Fostair was established prior to the subsequent cost analysis. There were no head-to-head clinical trials comparing Flutiform to Fostair.

The relevance of this comment to the materials at issue was unclear. The leavepieces specifically discussed the potential for use of Flutiform in place of Seretide Evohaler. Further, the data on file itself clearly stated at the outset that ‘No direct comparative studies between [Flutiform] and [Fostair] have been conducted’.

ii. Fostair could also be used at a dose of 1 puff twice daily and cost less than Flutiform at the lowest dosing level. In addition Seretide 500 Accuhaler cost less at the highest dosing level. Both of these pertinent clinical possibilities had been excluded from the analysis.

Again, the relevance of this comment to the material at issue was unclear. Neither Fostair nor Seretide Accuhaler were discussed within the leavepieces.

iii. There were some patients who could not be switched to Flutiform or who would require additional consultation and prescription costs which had not been accounted for in the analysis (eg patients who used a Volumatic Spacer or who were unable to use inhalers containing ethanol).

Napp noted that it had already discussed the issues surrounding the use of a Volumatic spacer and inhalers containing ethanol (Point 3 above). The data on file clearly set out how the figures used within the cost-minimisation analysis were calculated:

'Scottish Prescription Cost Analysis (PCA) was used to find the market share of the chosen MDIs in Scotland. These dispensed quantities are for all ICS/LABA combination units dispensed in primary care for both asthma and COPD. Cegedim Strategic Data (CSD) was used to ascertain the percentage of inhalers for [Seretide] and [Fostair] for asthma only and for patients over the age of 12 (comparable to low- and mid-dose [Flutiform]) and patients over the age of 18 (comparable to high-dose [Flutiform]). This is in line with the licensed indication for [Flutiform].'

iv. Consultation costs or the consequences of worsening asthma control in the absence of a consultation were not incorporated within the analysis, nor within the potential savings within the leavepiece itself.

Napp noted that cost-minimisation analysis was defined as:

'Where the consequences of two or more treatments or programmes are broadly equivalent, so the difference between them reduces to a comparison of cost'.

Consequently only medicine costs were included in subsequent calculations. Napp also noted that leavepiece 2 clearly stated the '**Potential** savings per annum' (emphasis added).

In summary, Napp considered that the claims were fair, accurate and balanced. Cost-effectiveness had been demonstrated and cost-minimisation analysis had been appropriately applied using medicine cost savings. The claims were substantiated and were not in breach of Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel noted that the claims at issue were referenced to Napp's data on file (UK/FLUT-12067 August 2012. HTA submission to support the cost-effectiveness of fluticasone propionate/formoterol fumarate MDI (metered-dose inhaler)) which Napp described as a cost-minimisation study. Only acquisition costs were compared. The Panel noted each party's submission on whether Bodzenta-Lukaszyk *et al* (2011a) demonstrated comparable efficacy and thus whether a cost-minimisation study was the appropriate analysis. In particular, the Panel noted that the study was an open-label, non-inferiority study; it had not been designed to demonstrate equivalence. The Panel also noted its rulings and comments above at Points 1 and 2 about Bodzenta-Lukaszyk *et al* (2011a) about patients' ages, doses and asthma severity. The Panel queried whether a cost-minimisation analysis was therefore appropriate.

The Panel noted that cost-minimisation studies were a legitimate activity, nonetheless any claims derived therefrom had to clearly reflect the analysis and not otherwise be misleading. The Panel considered that a reader would expect the claim 'cost-effectiveness' in the absence of further qualification, to mean more than a simple comparison of acquisition costs. In each leavepiece subsequent and distinct

sections discussed comparative acquisition costs thus compounding the impression that 'cost-effectiveness' was different and broader than a simple cost comparison. In leavepiece 2 the first bullet point about the economic burden of asthma referred both to the overall annual cost to the NHS of £1billion and the 'estimated annual drug cost for asthma' of £115million, thus highlighting the impact of indirect costs.

The Panel considered that the claims 'Improved cost-effectiveness' in leavepiece 1, '... a cost-effective treatment for asthma management' and '... a cost-effective treatment choice ...' in leavepiece 2, each implied that matters broader than acquisition cost had been compared. In addition the Panel noted its concerns about the cost-minimisation study and its reliance on Bodzenta-Lukaszyk *et al* (2011a) as set out above. The claims were thus each misleading and incapable of substantiation. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled in relation to each.

6 Cost claims

Leavepiece 2 contained the claims 'cost-effective treatment for asthma management' and 'a cost-effective treatment choice when ICS/LABA combination inhalers were being considered at Step 3 or 4 of the SIGN/BTS guidelines'. The Napp data on file was cited in support of both.

COMPLAINT

GlaxoSmithKline submitted that there was a range of other products and devices available for 'asthma management' and at 'Step 3 or 4 of the BTS/SIGN guidelines'. These had not been included within the leavepiece, nor were they included within the Napp data on file cited in support of the claims. This was of particular relevance as some of these products cost less than Flutiform.

GlaxoSmithKline submitted that the leavepiece advised switching. The switching of inhaled medication and inhalers was a complex process as it involved reviewing and educating the patient on the technique required for operating the new inhaler effectively. It also required a further follow-up review of the patient to ensure not only that asthma control was maintained but also that the patient was able to continue to use the inhaler properly.

No evidence was presented in the leavepiece to demonstrate that asthma control was maintained if/when patients were switched. Consequently the claims for potential annual savings did not take into account the costs associated with the necessary additional clinical interactions required with patients when they had their medicines changed or the potential costs associated with the risk of any resultant exacerbations.

In addition, the data presented were stratified by age; however, there were many patients who could not be switched to Flutiform who had not been considered eg patients who used a Volumatic spacer or those who were unable to use inhalers containing ethanol. Furthermore, the Napp data on file did not include

the full range of products and devices and thus could not substantiate the above claims. GlaxoSmithKline thus alleged that the claims and the accompanying table were in breach of Clauses 7.2 and 7.3.

RESPONSE

Napp stated that leavepiece 2 referred to Flutiform as a 'cost-effective treatment for asthma', and that it 'provides the clinician with a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Steps 3 and 4 of the SIGN/BTS guidelines'. These statements were supported by the results of the Napp cost-minimisation model.

It was entirely appropriate to use Seretide Evohaler as the comparator within the table for the following reasons:

- Seretide Evohaler was a widely used pMDI in the UK
- Flutiform and Seretide Evohaler had been directly compared in a clinical study.

As discussed in Point 5 above, cost-minimisation analysis was defined as: 'Where the consequences of two or more treatments or programmes are broadly equivalent, so the difference between them reduces to a comparison of cost.' Consequently, only medicine costs were included in the calculations. Napp submitted that its data on file clearly set out how the figures used within the cost-minimisation analysis were calculated.

Napp submitted that leavepiece 2 did not use the words 'drug switching', although the licensed indication was presented as part of the introduction to Flutiform. This included the possibility of prescribing Flutiform to either new patients not adequately controlled on their existing medication or for existing patients on Seretide Evohaler or another appropriate ICS/LABA combination (ie switch). Napp acknowledged that switching inhalers might not be simple and might have associated indirect costs incurred by clinical interactions or increased exacerbations. However, there might also be additional savings above those simply due to the cost of the inhaler, including reduced clinical interactions, and reduced exacerbations as a result of improved asthma control on switching. Hence Napp had been careful to state potential cost savings in leavepiece 2, and not advocate either starting all new asthma patients (inadequately controlled) or switching patients to Flutiform from another ICS/LABA inhaler.

With regard to patients using a Volumatic spacer device and patients unable to use inhalers containing ethanol, Napp referred to its response to Point 3 above. Napp also noted that there was no assumption within the leavepiece that all patients would be switched from Seretide Evohaler to Flutiform. Importantly the table looked at 25%, 50% and 75% of inhalers moving to Flutiform and did not include a 100% column. The table analysed potential cost-savings if patients switched, therefore it did not advise general switching.

Napp therefore submitted that the potential savings in the table were not misleading. The table clearly stated potential cost savings and was clearly labelled to define that the saving referred to medicine costs, by labelling the medicine and the cost.

In conclusion, using Seretide Evohaler as a comparator was justified, Napp did not assume all patients could switch and the table was factually accurate and not misleading. There was no breach of Clauses 7.2 or 7.3.

PANEL RULING

The Panel noted GlaxoSmithKline's allegation that the claims '... cost-effective treatment for asthma management' and 'a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Steps 3 or 4 of the SIGN/BTS guidelines' were misleading as other relevant products, some of which were less expensive than Flutiform, were not included in the Napp data on file analysis. This allegation had not been considered at Point 5 above.

The Panel noted that the heading of leavepiece 2 was a broad unqualified claim that Flutiform was a cost-effective treatment for asthma management when compared with all other relevant products. The comparison was not limited to that with Seretide Evohaler. The Panel noted its general comments on this claim at Point 5 above. The Panel considered that the heading 'flutiform...as a cost-effective treatment for asthma management' was misleading as alleged on this narrow point and a breach of Clause 7.2 was ruled.

The Panel noted that the claim 'flutiform provides the clinician with a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Steps 3 or 4 of the SIGN/BTS guidelines' was the sole bullet point in a section headed 'Rationale for flutiform'. The Panel noted the heading of leavepiece 2 and its comments thereon above and did not consider that the section in question was necessarily limited to a comparison with Seretide Evohaler as inferred by Napp; Seretide was not the only other ICS/LABA combination inhaler which could be used at Steps 3 or 4 of the SIGN/BTS guidelines. In the Panel's view the claim in question implied that Flutiform was a cost-effective choice when compared with all other ICS/LABA combination inhalers used at Steps 3 or 4 of the guidelines. It was not limited to a comparison with the Seretide Evohaler as alleged and was misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the table within the section headed 'Potential savings per annum' compared the cost savings, based on acquisition costs if 25%, 50% or 75% of patients on Seretide Evohaler 50, 125 and 250 were switched to Flutiform. In the Panel's view the table did not advocate switching *per se* as alleged by GlaxoSmithKline. It merely set out the potential savings based on acquisition costs in the event of a switch to the Seretide Evohaler. In the Panel's view, the basis of the comparison was clear and was not misleading as alleged. No breaches of Clauses 7.2 and 7.3 were ruled.

7 Table headed 'Can flutiform offer a range of strengths and savings?'

Page 3 of leavepiece 1 was headed 'Can Flutiform offer a range of strengths and savings?', and featured the table below.

	flutiform (fluticasone/ formoterol)		Seretide Evohaler (fluticasone/ salmeterol)		flutiform Drug cost savings
	Strength	Cost	Strength	Cost	
High	250/10ug	£45.56	250/25ug	£59.48	£13.92
Medium	125/5ug	£29.26	125/25ug	£35.00	£5.74
Low	50/5ug	£18.00	50/25ug	£18.00	£0.00

COMPLAINT

GlaxoSmithKline stated that in leavepiece 1 a claim of cost-effectiveness lay adjacent to a cost comparison of the three different strengths of Seretide Evohaler and Flutiform. Cost-effectiveness compared with Evohaler had not been demonstrated as discussed at Point 6 above. Given that cost-effectiveness had not been demonstrated, the juxtapositioning of this statement next to a cost comparison table that was itself not balanced, was misleading.

The cost comparison table only compared Flutiform with Evohaler. GlaxoSmithKline noted that alternative products were also available: Seretide Accuhaler (salmeterol/ fluticasone, GlaxoSmithKline), Symbicort (budesonide/ formoterol, AstraZeneca) and Fostair (beclomethasone/ formoterol, Chiesi) were also indicated for the maintenance treatment of asthma at Step 3 and 4 of the BTS/SIGN guidelines. Furthermore, the omission by Napp of the Seretide Accuhaler prices, particularly the high strength, appeared deliberate to conceal the fact that the Seretide 500 Accuhaler was a less expensive alternative to Flutiform 250/10µg.

In inter-company dialogue, Napp submitted that the Seretide Evohaler was the most appropriate comparator because clinical data vs Seretide Evohaler had been presented within leavepiece 1. GlaxoSmithKline disagreed with Napp's position and noted that the appropriate information referenced to Bodzenta-Lukaszyk *et al*, (2011a) for the mid/ low doses comparisons was missing from the cost comparison table. The reader was thus unaware that the rationale for this cost comparison was based solely upon non-inferior FEV1 results over a 12 week period in adults.

Whilst GlaxoSmithKline acknowledged that Napp's rationale for only directly comparing the two products, when other products were available, was because head-to-head data existed, it must be clearly acknowledged that data only existed for the low and medium doses of the inhaler, in 18 year olds and in an open label study that did not include severe patients.

As previously highlighted, Seretide Evohaler and Flutiform differed in many aspects; licensed

age ranges, alcohol content and spacer device usage. None of these had been made clear within leavepiece 1 which implied that all patients could be prescribed Flutiform instead of Seretide Evohaler. Clearly, this was not the case and Napp was obliged to present these important differences in a fully transparent and balanced way.

In summary, GlaxoSmithKline alleged that the cost comparison table was misleading, not accurate, fair or balanced and in breach of Clauses 7.2 and 7.3.

RESPONSE

Napp submitted that it had already explained in responses to Points 2, 4, 5 and 6 above that Flutiform had comparable clinical efficacy, was cost-effective and an appropriate option for use instead of Seretide Evohaler.

Positioned under the title header 'Can flutiform offer a range of strengths and savings?', the table clearly demonstrated the range of Flutiform's strengths and its respective costs, which were juxtaposed against the common details of Seretide Evohaler, with a further adjacent column clearly titled 'flutiform Drug cost savings'.

Seretide Evohaler and its range of strengths (and consequent pricing) was specifically chosen and placed against the entries of Flutiform, as it was rational that Flutiform and its range of strengths (and consequent pricing) should be placed in the most appropriate clinical context in the table by juxtaposing it with its most similar product, ie a medicine used for the same needs or intended for the same purpose. It was further appropriate, for the following reasons, to juxtapose specifically Seretide Evohaler against Flutiform, as there was direct clinical comparative data available and both were pMDIs, had three clinical doses, contained the same labelled dose of fluticasone and had dose counters.

It was also important in the context of savings to the NHS and clinicians that the Seretide Evohaler was the most commonly prescribed ICS/LABA combination pMDI in the UK and had cost the NHS over £300 million per annum for each of the last five years. This further strengthened the case for Seretide Evohaler's inclusion in the table set in the context against the Flutiform range, as cost was a highly relevant consideration for prescribers.

With regard to the other potential/possible inhalers that had been suggested for inclusion in the table, in addition to the fact that Napp did not have comparative evidence, Napp noted the following:

- Fostair was only available in one strength and in two treatment doses and so could not be appropriately set out as it stands in the current table against Flutiform and its full range of clinical doses. Thus, Fostair had not been included in the table.
- Seretide Accuhaler was a DPI which was a totally different delivery device system and required a different technique for inhalation. Seretide Accuhaler also only required one puff for dosing in contrast to the two puffs needed for

Flutiform dosing. In addition and importantly, Seretide Accuhaler was indicated not only for the treatment of asthma, but also for chronic obstructive pulmonary disease (COPD). Napp considered that these fundamental differences between Flutiform and Seretide Accuhaler, namely in the device delivery system, inhalation technique, dosing regimen, and in therapeutic indications, were significant enough for clinicians to perceive these two inhalers as two distinctly different medicines for use in different clinical contexts. Therefore, Napp considered that the inclusion of Seretide Accuhaler in the current table would be inappropriate, and its inclusion would confuse the clinician (and ultimately the patient). Thus, Seretide Accuhaler had not been included in the table;

- For similar reasons, Symbicort (a DPI) had not been included in this table, as stated above for Seretide Accuhaler, namely differences in device design (pMDI vs DPI), inhalation technique, therapeutic indication (asthma only vs asthma and COPD) and dosing regimens (of which Symbicort additionally included a SMART licence). Thus, Symbicort had not been included in this table.

Lastly, the focus of the clinical data package as detailed in the leavepiece, was vs Seretide Evohaler and so Napp considered it was appropriate to show only Seretide Evohaler in this table. The addition of other, and distinctly different, inhaler medicines without any previous mention in the leavepiece would be inappropriate and confuse the clinician.

Napp had also addressed in other responses the age ranges and spacer device used for Flutiform in leavepiece 1. It was not implied in either leavepiece that all patients could be prescribed Flutiform instead of Seretide Evohaler. The factual and comparative data had been presented in a fair and balanced way.

In summary, Napp submitted that the information on page 3 of leavepiece 1 was accurate, clear and noteworthy, fair and balanced, and importantly, clinically relevant, and therefore not in breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted its rulings above at Point 5 in relation to the claim 'Improved cost-effectiveness'. That claim was a bullet point beneath a prominent subheading and page heading. It was not 'next to' the cost comparison table on the facing page as GlaxoSmithKline alleged, nor was it within that table's immediate visual field. The Panel, whilst noting its ruling at Point 5, did not consider that the position of the claim 'Improved cost-effectiveness' on page 1 in relation to the table on page 2 was, in itself, misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel considered that the basis of the comparison in the table was clear, the acquisition costs of flutiform 250/10mcg/, 125/5mcg/, 50/5mcg were compared with those of Seretide Evohaler 250/25mcg, 125/25mcg and 50/25mcg. There was no implication that all patients could be prescribed

Flutiform instead of Seretide Evohaler, as alleged. Nor was it unacceptable to directly compare the acquisition costs of products if the basis of that comparison was abundantly clear. The table was not misleading as alleged. No breach of Clauses 7.2 and 7.3 was ruled.

8 Claim 'flutiform has a simple dosing schedule administered as 2 puffs, twice daily'

The claim at issue appeared in leavepiece 1 beneath the table referred to in Point 7 above and was referenced to the SPC.

COMPLAINT

GlaxoSmithKline stated that the leavepiece compared both clinical and economic aspects of Seretide Evohaler and Flutiform. The claim at issue appeared directly below the table at issue above.

In a comparative leavepiece designed to present the reasons why Flutiform should be prescribed instead of Seretide, the juxtaposition of the above statement directly below a comparative table implied that Seretide's dosing schedule was not simple or not as simple as Flutiform. This was not the case as the dosing schedules for the two inhalers were the same.

The use of the term simple to describe a dosing schedule was both a promotional claim and a hanging comparison and therefore required substantiation. Alternative, simpler dosing schedules for asthma were available and indeed Seretide Accuhaler was prescribed as one puff twice a day. Napp did not provide evidence to demonstrate that patients viewed a dosing schedule of two puffs twice a day as being simple but, in inter-company dialogue, advised that 'It ... is a plain statement of fact in terms of the dosing schedule for Flutiform being simple'.

As a result, GlaxoSmithKline alleged that, within material which compared Seretide with Flutiform, claims of a simple dosing schedule for Flutiform when the dosing schedules were the same was misleading. Furthermore, as simpler dosing schedules were available, a claim of simple was not accurate or balanced, was misleading and in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Napp submitted that leavepiece 1 provided health professionals with factual statements about Flutiform (ie all of page 1, wording beneath inhaler image on page 2, and the three statements beneath table on page 3). Throughout inter-company dialogue Napp had disagreed with GlaxoSmithKline's suggestion that the entire contents of the leavepiece were comparative.

The claim 'Flutiform has a simple dosing schedule administered as 2 puffs, twice daily' was one of three factual statements positioned beneath the table on page 3 of the leavepiece entitled 'Can Flutiform offer a range of strengths and savings?'. There was no implication that the first fact (simple dosing schedule) was any different from the adjacent two

facts 'Each inhaler contains 30 days' supply, 120 actuations = 60 doses' and 'Licensed for use with an AeroChamber Plus Spacer' – indeed all three facts applied equally to Seretide Evohaler and Flutiform.

The Oxford English Dictionary (OED) defined 'simple' as:

- 'easily understood',
- 'plain, basic or uncomplicated in form, nature or design; without much decoration or ornamentation.'

Napp maintained that 2 puffs, twice daily was both easily understood and uncomplicated. The word 'simple' was an adjective. 'Simple' was not the comparative or the superlative when 'simpler [than]', or 'simplest' would be used.

There was not, as implied, a comparative statement to Seretide Evohaler, and Napp had not used a hanging comparison as alleged ie the word, 'simpler', was not used. Furthermore, Napp did not imply that the dosing schedule for Seretide Evohaler was in any way more complicated than the dosing schedule for Flutiform.

In the context of other asthma management regimes 2 puffs, twice daily of an inhaler was simple. Napp agreed with GlaxoSmithKline that Seretide Evohaler had the same simple dosing schedule.

In summary, Napp maintained that simple was not used as a comparison, there was no use of hanging comparisons, no use of the word 'simplest' or 'simpler [than]'. The definition of 'simple' was as given by the OED. Taken in context with the two factual statements placed immediately adjacent to it, Napp asserted that the use of 'flutiform has a simple dosing schedule administered as 2 puffs, twice daily', which included the word 'simple', was accurate, fair and balanced, and therefore was not in breach of Clauses 7.2, 7.3, and 7.4.

PANEL RULING

The Panel noted that the claim in question appeared in small print beneath the comparative table at issue in Point 7 which comprised most of the page. The Panel considered that the claim would be considered by readers in the context of the overall comparative message of the page and thus it implied that Seretide Evohaler did not have a simple dosing schedule and that was not so. Seretide Evohaler had the same dosing schedule as Flutiform. The claim was misleading in this regard and incapable of substantiation. A breach of Clauses 7.2, 7.3 and 7.4 was ruled.

The Panel considered that the claim indirectly compared the dosing schedule of Flutiform with Seretide Evohaler. The Panel therefore did not consider the claim was a hanging comparison as alleged. Nor was it misleading because other products with simpler dosing schedules were available as alleged by GlaxoSmithKline. The Panel considered that the claim in question was not misleading on these points as alleged. No breach of Clauses 7.2 and 7.3 was ruled.

9 Clauses 8.1, 9 and 2

COMPLAINT

GlaxoSmithKline submitted, given the totality of the multiple issues raised and unresolved through extensive inter-company dialogue, that collectively the two leavepieces disparaged Seretide in breach of Clause 8.1. In addition, given the seriousness and number of breaches, the failure to maintain high standards and the potential to encourage Flutiform prescribing outside the marketing authorization and impact upon patient safety, the two leavepieces constituted an additional breach of Clauses 2 and 9.1.

RESPONSE

Napp firmly believed that it had fully addressed the multiple issues raised by GlaxoSmithKline during inter-company dialogue as well as in this response. The two leavepieces did not disparage Seretide Evohaler and were not in breach of Clause 8.1. Napp submitted that it had maintained high standards and did not encourage the prescribing of Flutiform outside of its marketing authorization nor compromised patient safety. Napp vigorously asserted that it had not breached multiple clauses including Clauses 2, 3, 7.2, 7.3, 7.4, 8.1, or 9.1.

PANEL RULING

The Panel noted its rulings above of breaches and no breaches of the Code. Whilst some comparisons had been considered misleading, the Panel did not consider that they went beyond that and disparaged Seretide Evohaler. No breach of Clause 8.1 was ruled.

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

Although noting its rulings above, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular disapproval of a company's material or activities. No breach of Clause 2 was ruled.

APPEAL FROM GLAXOSMITHKLINE

GlaxoSmithKline alleged, given the number of issues raised and unresolved through extensive inter-company dialogue and the number of breaches of the Code ruled by the Panel, that in addition to failing to maintain high standards, these two leavepieces also breached Clause 2.

As acknowledged by the Panel, the information within the leavepieces was insufficiently complete to be certain that the reader could accurately interpret the claims and thereby appropriately prescribe Flutiform within its marketing authorization:

Point 1

'.....the Panel considered the broad unqualified claim "comparable efficacy" implied more than a measurement of FEV1'.

'The Panel considered that the broad unqualified claim "Comparable clinical efficacy (P=0.007, open label)" implied that Flutiform could be used in all of those patients for whom Seretide might be prescribed and that there was robust comparative clinical data in relation to all doses and patient populations and that was not so. The Panel noted that there was some comparative efficacy data but considered that insufficient information about the study had been provided to enable the reader to accurately interpret the claim which was consequently misleading and incapable of substantiation'

Point 3

'No information was given about when such a substitution would be appropriate. The Panel noted that Flutiform was not a suitable substitute for patients aged between 4 and 11 years who could be treated with Seretide Evohaler'. The Panel considered that in the absence of information to the contrary, readers would assume that Flutiform could be substituted for Seretide Evohaler in all circumstances and that was not so'

GlaxoSmithKline stated in relation to the Panel's comments above that:

- the absence of such key information did not enable the prescriber to make a fully informed decision regarding the appropriate prescribing of Flutiform for their patients
- the claims of clinical comparability had not been suitably qualified to represent the current level of evidence to allow the reader to accurately interpret the claims
- no information was provided to the prescriber to advise when substitution from one treatment to another would be appropriate
- in the absence of information to the contrary, readers would assume that Flutiform could be substituted for Seretide Evohaler in all circumstances and that was not so

not only posed a risk to patient safety, but pointed to the fact that Napp had promoted outside of the licensed indication for Flutiform.

GlaxoSmithKline contended that this, together with the twenty breaches of the Code ruled by the Panel, brought the industry into disrepute in breach of Clause 2.

COMMENTS FROM NAPP

Napp was very disappointed that GlaxoSmithKline had appealed the Panel's ruling of no breach of Clause 2 and queried its reasons for doing so, given the Panel's careful and detailed assessment.

Napp submitted that given the extent and duration of this complaint, for the sake of clarity, the history was as follows. In September 2012 Napp launched Flutiform onto the UK fixed-dose combination respiratory market, a market worth around £700 million per annum, dominated by GlaxoSmithKline with annual sales from Seretide Evohaler exceeding £300 million.

Napp submitted that prior to the launch of Flutiform, the leavepieces, together with other promotional materials, were pre-vetted by the MHRA; amendments were made and accepted. The MHRA reviewed the data sets relevant to GlaxoSmithKline's complaint and raised no significant concerns. The MHRA saw the final versions of the two leavepieces in question. This was important given GlaxoSmithKline's allegation that Napp had compromised patient safety and promoted outside of the Flutiform licence.

Napp submitted that within the first week of launch, GlaxoSmithKline had contacted Napp about leavepiece 2 (ref UK/FLUT 11023a), aimed at NHS payers, as it had significant cost savings over Seretide Evohaler at the medium and high doses. By the end of the second week of launch, GlaxoSmithKline had written to Napp about both of the leavepieces now at issue; the company challenged ten points and alleged twenty eight breaches of the Code.

Napp submitted that in the extensive inter-company dialogue which ensued, it made every effort to find a solution to the allegations. However GlaxoSmithKline only accepted Napp's proposed amendments in respect of two of the ten points. Furthermore, during inter-company dialogue GlaxoSmithKline failed to answer an important and relevant question about the licensed age ranges and device in its GOAL study and GlaxoSmithKline's Seretide promotional materials. GlaxoSmithKline stated that if Napp would like to raise the new point in a separate complaint, it would be happy to provide a detailed response. The significance of this was that Napp acted reasonably and tried to find an acceptable solution which GlaxoSmithKline would not entertain, despite the fact it did not make such matters clear in its own promotional materials.

Napp submitted that following unsuccessful completion of inter-company dialogue, GlaxoSmithKline introduced major new points contrary to the requirements of Paragraph 5.3 of the Constitution and Procedure. Notwithstanding GlaxoSmithKline's failure to follow due process, Napp discussed this with the PMCPA and agreed to respond, albeit within additional time which was needed given the new points raised. The Panel reviewed each company's arguments and made its rulings, which Napp had accepted and which GlaxoSmithKline had now appealed.

Napp noted that GlaxoSmithKline had appealed against the ruling of no breach of Clause 2 mainly because of the multiple issues raised and unresolved through extensive inter-company dialogue and the cumulative number of breaches of the Code. Napp vigorously disputed both of these points.

Napp submitted that to suggest that Clause 2 should be applied because of the number of issues 'unresolved through extensive inter-company dialogue' was illogical, as all inter-company complaints to the PMCPA should only occur after unresolved inter-company dialogue. If a matter was resolved through inter-company dialogue, then there would not be a complaint to PMCPA. Inter-company dialogue was a procedural step and the failure to

agree a matter at this stage in and of itself should have no bearing on whether Clause 2 had been breached.

Moving to GlaxoSmithKline's second reason 'cumulative number of breaches', Napp noted that the Panel had ruled breaches of Clauses 7.2, 7.3, 7.4 and 9.1 but no breaches of 2, 3.2 or 8.1. GlaxoSmithKline correctly stated that there were twenty breaches ruled, but ignored the fact that several of the breaches concerned the same matter (see below) and that the Panel also ruled against thirteen of GlaxoSmithKline's complaints. The twenty breaches related to eight grounds of complaint, of which two were found not to be valid and two were upheld in part only:

- For the claim 'comparable clinical efficacy' there were two breaches, each, of Clauses 7.2, 7.3 and 7.4
- For the claim 'the efficacy and tolerability of flutiform were sustained for up to 12 months' there was a breach of Clause 7.3
- For the question 'why should I prescribe flutiform instead of Seretide Evohaler?' there was a breach of Clauses 7.2, 7.3 and 7.4
- For the claim 'Faster onset of action' there was no breach of Clauses 3.2, 7.2, and 7.4
- For cost-effectiveness claims, breaches of Clauses 7.2, 7.3 and 7.4 were ruled
- For cost claims there was a breach of Clause 7.2 on a narrow point, breaches of Clause 7.2 and 7.3 and no breach of Clauses 7.2 and 7.3
- For the table headed 'Can flutiform offer a range of strengths and savings?' there was no breach of Clause 7.2 and no breach of Clauses 7.2 or 7.3
- For the claim 'flutiform has a simple dosing schedule administered as 2 puffs, twice daily' there was a breach of Clause 7.2, 7.3 and 7.4 but no breach of 7.2 and 7.3
- For Clauses 8.1, 9.1 and 2, there was a breach of Clause 9.1 but no breaches of Clauses 8.1 or 2

Turning to GlaxoSmithKline's specific points:

- Point 1 – The first quotation from the Panel provided was selective and did not properly summarise the entire position and ruling on comparable efficacy, as the Panel further noted that the secondary outcome data showed that Flutiform and Seretide were similar in a number of additional relevant efficacy measures.
- Point 1 – Again the second quotation failed to fully represent the Panel's opinion on the point under discussion.
- Point 3 – The focus on providing further clarity had been accepted by Napp, and Napp again noted that GlaxoSmithKline also did not make it clear in its materials – a point it failed to respond to when questioned during inter-company dialogue.

Napp noted the supplementary information for Clause 2, which stated that:

'A ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances.'

Examples of activities that are likely to be in breach of Clause 2 include prejudicing patient safety and/or public health, excessive hospitality, inducements to prescribe, inadequate action leading to a breach of undertaking, promotion prior to the grant of a marketing authorization, conduct of company employees/agents that falls short of competent care and multiple/cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.'

Napp firmly refuted GlaxoSmithKline's allegation that it had promoted Flutiform outside of its licence and specifically noted that the Panel ruled no breach of Clause 3.2. No breach of Clause 4 (failure to disclose prescribing information and obligatory information) had been alleged which indicated that no pertinent safety information had been omitted. Furthermore, the Panel also ruled that Napp did not disparage the Seretide Evohaler and was therefore not in breach of Clause 8.1.

The multiple breaches of 7.2, 7.3, 7.4 and the single breach of 9.1 ruled by the Panel had been at a single point in time, related to very similar claims, and were not repeated occurrences.

Napp submitted that fundamentally the complaint was about the possibility that the claims in question could mislead the reader. The Panel's rulings of breaches of the Code indicated that in order to use the claims at issue, additional qualification/clarification was needed and care with respect to juxtaposition of claims and font size was required. Although Napp never intended to make any promotional claims in breach of either the letter or the spirit of the Code, it accepted these rulings and thanked the Panel for its detailed review of its materials and arguments and understood that this had been a lengthy process. The Panel carefully considered and concluded on each point and articulated its decision and reasoning in full. Napp was therefore happy that the Panel's decision was considered and fair. The Panel was correct to rule no breach of Clause 2; Napp regretted that the Appeal Board now needed to expend time and effort in the appeal of this ruling.

FINAL COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline stated that the decision to appeal the Panel's ruling of no breach of Clause 2 was not taken lightly. After carefully considering the facts surrounding this complaint, GlaxoSmithKline alleged that Napp's activities posed a risk to patient safety. It was regrettable, that on this occasion, GlaxoSmithKline had considered it necessary to refer this matter to the Appeal Board.

GlaxoSmithKline did not agree that its quotations of the Panel's rulings were selective, as it clearly stated 'The Panel noted that there was some comparative efficacy data.....', and thus summarised the entire position of the Panel ruling with regard to secondary endpoints.

GlaxoSmithKline noted that during inter-company dialogue Napp had raised a point of clarification

with regard to GlaxoSmithKline's material. In order not to confuse matters, GlaxoSmithKline requested written details from Napp to enable it to appropriately assess the query and respond. However, GlaxoSmithKline did not receive this written response and was surprised that this matter had been raised with the PMCPA six months later, contrary to the requirements of Paragraph 5.3 of the Constitution and Procedure.

In addition GlaxoSmithKline noted the following statements made by Napp in its comments on the appeal:

- 'GlaxoSmithKline only accepted Napp's proposed amendments in respect of two of the ten points'

GlaxoSmithKline stated that the two claims referred to by Napp were: 'Fluticasone and Formoterol in a fixed dose combination' and 'A comparable range of strengths in a familiar yet modern MDI'.

During a teleconference, GlaxoSmithKline and Napp discussed both claims in detail and no such amendments were proposed by Napp; nor were such proposed amendments submitted to GlaxoSmithKline. In the spirit of inter-company dialogue, GlaxoSmithKline was prepared to accept Napp's initial response about these two claims, and neither of these points were escalated to the PMCPA. At present both claims still featured in a different leavepiece (ref UK/FLUT-11050). GlaxoSmithKline therefore contested Napp's suggestion that amendments were proposed or indeed made.

- 'GlaxoSmithKline introduced major new points'

GlaxoSmithKline stated that the points to which Napp referred related directly to the original complaint regarding the claim 'comparable clinical efficacy'. GlaxoSmithKline did not agree that new points were raised. The points in question challenged the bioavailability, clinical evidence to demonstrate comparable clinical efficacy, patient selection and dosage selection of Flutiform studies. GlaxoSmithKline reminded Napp that it originally referred to all of these points in its correspondence. All points discussed within GlaxoSmithKline's complaint were provided as rationale scientific arguments to substantiate its concerns with regard to this claim that Flutiform was 'clinically comparable' to the Seretide Evohaler. GlaxoSmithKline noted that some of its materials had been pre-vetted by the MHRA. However, the clinical data package which accompanied a newly launched medicine was substantial and could often be complex. Therefore as an industry that operated through self-regulation, it had a responsibility to ensure it maintained the high standards that were expected by patients, health professionals and society. It might be appropriate for a company to raise concerns about the activity of a fellow company and this was how it ensured continued self-regulation and continued to ensure high standards.

GlaxoSmithKline submitted that key information to enable prescribers to make fully informed decisions

of the appropriate prescribing of Flutiform for their patients had been excluded and claims of clinical comparability had not been suitably qualified to represent the current level of evidence. Ultimately, these significant issues put patient safety at risk, which collectively, with twenty breaches of the Code ruled by the Panel, constituted a breach of Clause 2.

APPEAL BOARD RULING

The Appeal Board noted that, prior to the hearing, GlaxoSmithKline had notified the Authority that it wanted to withdraw its appeal. This was as a result of further inter-company dialogue. Napp subsequently confirmed its agreement that the appeal should be withdrawn. GlaxoSmithKline, however, had notified the Authority after it had received Napp's response to GlaxoSmithKline's appeal and thus in accordance with Paragraph 15.2 of the Constitution and Procedure, the appeal could not be withdrawn. Both parties were so advised. The Appeal Board further noted that, in response to questioning, both companies maintained their position that they would have wished the appeal to be withdrawn.

The Appeal Board was concerned about the multiplicity of breaches ruled in the two leavepieces. However, although twenty breaches of the Code were ruled many of the matters overlapped. The two leavepieces were part of the same (launch) campaign for Flutiform and so in that regard the breaches had occurred in parallel; Napp had not repeated breaches of the Code from one campaign to another and over a period of time.

The Appeal Board was further concerned that the leavepieces might have encouraged the use of Flutiform in patients for whom it was not indicated and also the inappropriate switching of patients from Seretide to Flutiform on the basis of, *inter alia*, cost. The Appeal Board considered, however, that prescribers would be well aware that asthma devices were not like-for-like and so direct substitution would be unlikely. In the Appeal Board's view when asthmatics were changed from one medicine to another, processes were established to ensure that patient safety was protected and prescribers would be reluctant to switch well-controlled patients.

The Appeal Board noted that the Panel had ruled a breach of Clause 9.1 as high standards had not been maintained. The Appeal Board noted its concerns about the breaches of the Code and the possible, theoretical adverse consequences of some of the claims on patient safety but considered that, on balance, the circumstances did not warrant a breach of Clause 2 and it upheld the Panel's ruling of no breach of that clause. The appeal was thus unsuccessful.

Complaint received

19 December 2012

Case completed

17 July 2013

VOLUNTARY ADMISSION BY SHIRE

Journal reprint

Shire Pharmaceuticals voluntarily admitted that a reprint from *The Lancet* (Mehta *et al* 2009), which it used to promote Replagal (agalsidase alfa), contained a bar chart which was misleading about Fabrazyme (agalsidase beta) marketed by Genzyme Therapeutics.

When Mehta *et al* was published in December 2009, Genzyme noted the incorrect bar chart. The lead author was contacted and *The Lancet* published a corrected figure in January 2010.

Shire submitted that it circulated official reprints within a reprint carrier, via its sales team and at conferences. The *Lancet* reprints comprised the original article with the correction at the end. Shire noted, however, that neither the reprint nor the reprint cover made it clear that the article contained an error. The uncorrected bar chart was still reproduced and the corrected bar chart was at the end of the article. Shire appreciated that without explicitly drawing attention to it, readers might not notice the correction.

The detailed response from Shire is given below.

The Panel noted that the bar chart at issue depicted decrease in renal function as measured by the mean yearly fall in estimated glomerular filtration rate (GFR) according to stage of chronic kidney disease at baseline in patients with Fabry's disease during five years of treatment with Replagal. One bar of the chart depicted data from Germain *et al* (2007) showing results for Fabrazyme which had been 'plotted for reference and comparison'. The bar for Fabrazyme showed a mean annualised change in GFR of approximately $-2.8\text{ml}/\text{min}/1.73\text{m}^2$. The change in GFR for Fabrazyme reported by Germain *et al* was in fact approximately $-1.1\text{ml}/\text{min}/1.73\text{m}^2$. Mehta *et al* did not compare Fabrazyme and Replagal in the text of their paper. The *Lancet* published a corrected bar chart on the last page of the reprint; to see the corrected bar chart the reader would have to turn over the last page of the paper although the Panel noted that it was clear from the last page 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 summary. The reprint folder cited the references for both the original paper and the corrected bar chart as did the front page of the summary. The 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 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 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 and no breaches of the Code, including Clause 2, were ruled.

Shire Pharmaceuticals Limited voluntarily admitted that a reprint from *The Lancet* (Mehta *et al* 2009) which it used in the promotion of Replagal (agalsidase alfa), contained a bar chart which was misleading about Fabrazyme (agalsidase beta) marketed by Genzyme Therapeutics. 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. Fabrazyme and Replagal were both indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry's disease.

COMPLAINT

Shire stated that when Mehta *et al* was published in December 2009, Genzyme noted that the bar chart in question (figure 4) contained an error which related to Fabrazyme. The lead author was contacted and *The Lancet* published a corrected figure in January 2010.

Shire noted that in inter-company dialogue it had stated that it would not deliberately refer to, or use the bar chart in its uncorrected form.

Shire submitted that as Mehta *et al* presented data about Replagal it acquired official reprints and circulated them, within a reprint carrier, via its sales team and at conferences. As was the standard practice when errors had been noted, *The Lancet* reprints comprised the original article with the correction at the end. Shire noted, however, that neither the reprint nor the reprint cover made it clear that the article contained an error. The uncorrected bar chart was still reproduced and the corrected bar chart was at the end of the article as per standard practice. It was possible, therefore, that readers might not notice the correction.

Shire immediately arranged for the sales team to return any remaining copies of the reprint. Shire submitted that while the reprints it used were the official versions obtained from *The Lancet*, it appreciated that in using them without explicitly drawing the readers' attention to the correction, they might not have noticed it.

When writing to Shire, the Authority asked it to respond in relation to Clauses 2, 7.2 and 9.1 of the Code.

RESPONSE

Shire explained that the Fabry Outcome Survey was a Shire sponsored, long-term, observational study of patients with Fabry's disease who were either not treated or who were receiving Replagal. The survey's international board, which was made up of independent physicians, decided to publish the results in a cohort of patients who had been treated for 5 years. The data was collated by Shire statisticians and presented to the authors. One of the ten authors was a health professional employed by Shire. The authors with writing support from an agency (paid for by Shire), completed the article and submitted it to The Lancet. As with all Shire-sponsored articles that were about one of its products, the article was internally reviewed to ensure accuracy of the Shire data but was not subject to any other editorial review by Shire. The involvement of Shire and Shire personnel was referenced in the article.

Following online publication of the article on 2 December, Shire received a letter from Genzyme which noted an error in the bar chart which referred to Fabrazyme. Genzyme stated that it had already contacted the lead author who was aware of the error and would ask The Lancet to correct it. The Lancet subsequently published a correction in its usual fashion (Department of Error).

In response to Genzyme's letter, Shire stated that it would not deliberately refer to, or use, the bar chart in its uncorrected form. However, it reserved the right to use the article when accompanied by the correction notice or any data including the corrected bar chart.

Shire stated that after the correction had been published it received 220 official reprints from The Lancet to be distributed in a reprint carrier that was certified on 21 August 2012. The reprint carrier also included an insert which the representatives were encouraged to focus on when they discussed the article. This insert did not refer to the bar chart but focussed on the conclusions drawn by the authors from the Fabry Outcome Study data. The reprint carrier referenced the original article and the correction. During the approval and certification process it was considered that the use of the official reprint including the corrected version of the bar chart would satisfy the agreement with Genzyme as to how the reprint would be used.

Shire stated that each of its five representatives received 20 copies of the reprint and carrier and distributed some at various 1:1 meetings and conferences. On 14 February 2013, following an email from Genzyme which had picked up one of these reprints at a meeting, the representatives were emailed and asked to return all remaining copies of the reprint carriers until the company had completed its investigation and resolved the situation.

Approximately 40 copies had been returned. Shire noted that the initial inter-company dialogue was conducted between 11 December 2009 and 8 February 2010 and the latest correspondence started 17 December 2012 and had been ongoing since then. Shire confirmed immediately that it had used the official reprint from The Lancet and not the uncorrected version. Shire accepted that the erratum could have been more clearly referenced although it was the standard reprint from The Lancet; further, the reprint carrier cited both the original reprint and the erratum. Whilst not currently incorrect, given the inability to reach consensus with Genzyme, Shire considered that the most reasonable approach would be to self-refer this issue to the Authority.

PANEL RULING

The Panel noted that the bar chart at issue depicted decrease in renal function as measured by the mean yearly fall in estimated glomerular filtration rate (GFR) according to stage of chronic kidney disease at baseline in patients with Fabry's disease during five years of treatment with Replagal. One bar of the chart depicted data from Germain *et al* (2007) showing results for Fabrazyme which had been 'plotted for reference and comparison'. The bar for Fabrazyme showed a mean annualised change in GFR of approximated -2.8ml/min per 1.73m². The change in GFR for Fabrazyme reported by Germain *et al* was in fact approximately -1.1ml/min per 1.73m². 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 last page of the paper although the Panel noted that it was clear from the last page 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 (ref UK/HG/REP/12/0008a). The reprint folder cited the references for both 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 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.

Complaint received **21 March 2013**

Case completed **16 April 2013**

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/1.73m²). 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/1.73m² 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/1.73m², 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 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. 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/1.73m² 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/1.73m² which was close to the rate of decline in estimated GFR observed in the normal population (approximately 0.8ml/min/year/1.73m²).

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/1.73m²). 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/1.73m² 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/1.73m², 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/1.73m².

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 α -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/1.73m² 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/1.73m² which was close to the rate of decline in estimated GFR observed in the normal population (approximately 0.8ml/min/year/1.73m²).

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

NOVO NORDISK v SANOFI

Promotion of Lyxumia

Novo Nordisk complained about claims in a leaflet, mailer and on exhibition panels used by Sanofi to promote Lyxumia (lixisenatide). Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist for the treatment of type 2 diabetes. It was indicated in combination with oral glucose lowering medicines and/or basal insulin when these, together with diet and exercise, did not provide adequate glycaemic control. Novo Nordisk marketed Victoza (liraglutide) which was also a GLP-1 receptor agonist for use in type 2 diabetes.

The detailed response from Sanofi is given below.

With regard to the claim 'The only once-daily prandial GLP-1 receptor agonist' Novo Nordisk alleged that as all GLP-1 receptor agonists reduced elevated blood glucose levels, including post-prandial glucose (PPG), through a glucose dependent mode of action the claim was not justified or substantiated by the available scientific evidence.

Novo Nordisk alleged that Sanofi had introduced the term '*prandial* GLP-1 receptor agonist' (emphasis added) with no clinical grounds for differentiation within the GLP-1 receptor agonist class, in an attempt to differentiate Lyxumia from Victoza and mislead health professionals. The Victoza summary of product characteristics (SPC) summarised evidence showing that Victoza reduced PPG in all three meals of the day. The same conclusion was made by Kapitza *et al* (2013). Sanofi inferred that any differences in PPG efficacy between Lyxumia and Victoza arose from profound differences in their action; ie Lyxumia strongly inhibited gastric emptying whilst Victoza had a negligible effect. This conclusion was reached based on inconclusive evidence and rodent studies were cited for Victoza. Clinical studies showed Victoza significantly delayed gastric emptying, but these were not cited by Sanofi.

Novo Nordisk stated that for Lyxumia to reliably be labelled as a 'once-daily prandial' agent, it had to reduce absolute prandial glucose levels across all meals. The available evidence could not support the PPG lowering effect of Lyxumia throughout the whole day. Sanofi refused to provide data to allow Novo Nordisk to assess whether Lyxumia demonstrated this efficacy. Sanofi had provided modified data.

Novo Nordisk therefore alleged that the claim 'The only once-daily prandial GLP-1 receptor agonist' was misleading as it implied greater efficacy than supported by the evidence and it disparaged Victoza.

The Panel noted that health professionals would be familiar with the term 'prandial' in the claim

that Lyxumia was 'The only once-daily prandial GLP-1 receptor agonist' but considered that GLP-1 receptor agonists were not commonly described as such. The Panel disagreed with Sanofi's submission that Lyxumia was widely described in the literature as a 'prandial GLP-1 receptor agonist'. The only paper submitted to describe Lyxumia in this way was Horowitz *et al* which was published in 2013; Sanofi had been involved in the production of the paper before it was peer reviewed. It was not stated whether the company had reviewed the paper. Given the authors' reference to the approval of Lyxumia by the European Medicines Agency in February 2013, the Panel queried whether the paper had been published before the mailer and the leaflet had been approved (7 and 5 February respectively). In the Panel's view, health professionals would not be familiar with 'prandial' as a description of a GLP-1 receptor agonists. Other authors only described GLP-1 receptor agonists as short- or long-acting. Short-acting GLP-1 receptor agonists, eg Lyxumia, produced a modest reduction in fasting blood glucose levels and a strong reduction in post-prandial glucose levels. Conversely, long-acting GLP-1 receptor agonists, eg Victoza, produced a strong reduction in fasting blood glucose levels and a modest reduction in post-prandial glucose levels. Thus both short- and long-acting GLP-1 receptor agonists affected fasting and post-prandial blood glucose levels but each had a greater effect on one or the other.

The Panel noted that Lyxumia and Victoza were both once-daily medicines. Therefore the claim that Lyxumia was the only once-daily prandial GLP-1 receptor agonist implied that Victoza had no prandial action at all. The Panel accepted that in a 28 day study, Lyxumia had been shown to decrease post-prandial glucose levels. Although the after breakfast (standardised test meal) data showed an advantage for Lyxumia compared to Victoza nonetheless, Victoza decreased post-prandial glucose levels (Kapitza *et al*). The Panel further noted that Section 5.1 of the Victoza SPC stated that '[Victoza] has 24 hour duration of action and improves glycaemic control by lowering fasting and post-prandial blood glucose in patients with type 2 diabetes mellitus'. The Lyxumia SPC stated 'When administered once daily, [Lyxumia] improves glycaemic control through the immediate and sustained effects of lowering both post-prandial and fasting glucose concentrations in patients with type 2 diabetes'.

The Panel considered that as the claim stated that Lyxumia was the only once-daily prandial GLP-1 receptor agonist, it implied that the only other once-daily GLP-1 receptor agonist, ie Victoza, had no prandial effect at all which was not so. The Panel considered that readers would be unfamiliar with the term 'prandial GLP-1 receptor agonist'.

The claim was misleading and exaggerated and the Panel ruled breaches of the Code. The claim disparaged Victoza by implying that it had no prandial action and a further breach of the Code was ruled.

Upon appeal by Sanofi, the Appeal Board referred to Section 5.1, Pharmacodynamic properties, of the Lyxumia SPC and noted that under a heading of 'Mechanism of action' only the last sentence referred to what Sanofi had referred to as the predominant mechanism of action of Lyxumia; delay in gastric emptying.

The Appeal Board noted Sanofi's submission that prandial meant 'pertaining to a meal' and that Lyxumia fitted this description in at least two ways – ie its predominant mechanism of action and its requirement to be given once daily, within the hour prior to the first meal of the day or the evening meal. The Appeal Board noted that Lyxumia lowered both fasting and post-prandial glucose concentrations. Victoza also had a dual mechanism of action. It was given once daily at any time, independent of meals. The Appeal Board did not consider that the term 'prandial' in the claim 'The only once-daily prandial GLP-1 receptor agonist' could be used to distinguish Lyxumia from Victoza. 'Prandial' in the claim at issue appeared to have a different meaning compared with when it was currently more usually used to describe insulins or glucose regulators (glinides). In the Appeal Board's view, health professionals would not understand what Sanofi meant by a 'prandial GLP-1 receptor agonist'; such medicines were more usually, and currently, differentiated in the literature as long-acting (Victoza) or short-acting (Lyxumia). The Appeal Board considered that the claim that Lyxumia was 'The only once-daily prandial GLP-1 receptor agonist' was misleading and exaggerated. The Appeal Board upheld the Panel's rulings of breaches of the Code. The Appeal Board further considered that the claim disparaged Victoza as it implied that Victoza had no prandial action which was not so. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal was thus unsuccessful.

Novo Nordisk alleged that the claim 'A positive addition can make all the difference' which appeared in the leavepiece and on the exhibition stand over-promised on the benefits that Lyxumia offered. No treatment could make all the difference and 'all' implied a greater improvement to a person with type 2 diabetes than simply a post-prandial glucose lowering effect over one meal in the day.

The Panel disagreed with Sanofi's submission that the claim related broadly to the treatment of diabetes and not directly to Lyxumia. The claim was an integral part of Lyxumia promotional material; it appeared adjacent to a picture of the Lyxumia pre-filled pen. 'Positive addition' was written in a font the same colour as the pen. In the Panel's view readers would associate the broad, unqualified claim with Lyxumia.

The Panel considered that as the claim was unqualified it was impossible to know what it meant

with regard to Lyxumia treatment; readers would interpret it in their own way. In that regard the Panel considered that the claim was misleading and exaggerated; breaches of the Code were ruled.

With regard to the claim 'Strong evidence supporting the use of Lyxumia as add-on to basal insulin', Novo Nordisk alleged that results from the cited references, Rosenstock *et al* (2012) and Riddle *et al* (2012), were insufficient to support the use of 'strong' and that the European Medicines Agency (EMA) appeared to hold a similar opinion.

The Panel noted that Lyxumia was indicated as adjunctive therapy and in that regard Sanofi would have had to submit evidence to the regulatory authorities that such use of Lyxumia was well tolerated and effective. The Panel considered that to describe such evidence as 'strong' implied some special merit – all evidence provided for the grant of any marketing authorization had to be robust. In that regard the Panel considered that the claim exaggerated the strength of the data and it ruled a breach of the Code.

Novo Nordisk Limited complained about the promotion of Lyxumia (lixisenatide) by Sanofi.

Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist for the treatment of type 2 diabetes. It was indicated in combination with oral glucose lowering medicines and/or basal insulin when these, together with diet and exercise, did not provide adequate glycaemic control. Novo Nordisk marketed Victoza (liraglutide) which was also a GLP-1 receptor agonist for use in type 2 diabetes.

The material at issue was a representatives' leavepiece (ref GBIE.LYX.13.01.14 (PRO 20055)); a one-off mailer (ref GBIE.LYX.13.02.02 (PRO 20140)) sent in February to inform health professionals about the availability of Lyxumia and to offer the opportunity for further product information and exhibition panels used at the Diabetes UK Annual Professional Conference, 13-15 March 2013. The leavepiece was withdrawn from use on 13 May 2013.

1 Claim 'The only once-daily prandial GLP-1 receptor agonist'

This claim appeared in the leavepiece, the mailer and on the exhibition stand.

COMPLAINT

Novo Nordisk stated that Victoza and Lyxumia were both once-daily GLP-1 receptor agonists. All GLP-1 receptor agonists effectively reduced elevated blood glucose levels, including post-prandial glucose (PPG), through a glucose dependent mode of action. Novo Nordisk alleged that the claim at issue was not justified or substantiated by the available scientific evidence.

Novo Nordisk alleged that Sanofi had introduced the term '*prandial* GLP-1 receptor agonist' (emphasis added) with no clinical grounds for differentiation within the GLP-1 receptor agonist class, in an

attempt to differentiate Lyxumia from Victoza and mislead health professionals.

The Victoza summary of product characteristics (SPC) summarised evidence to show Victoza effectively reduced PPG in all three meals of the day. The same conclusion was made by Kapitza *et al* (2013).

With regard to gastric emptying of Victoza and Lyxumia, Sanofi inferred that any differences in PPG efficacy between the two medicines arose from profound differences in their action; ie Lyxumia exerted a strong inhibition of gastric emptying, whilst Victoza exerted a negligible effect on gastric emptying. This conclusion was reached based on inconclusive evidence and rodent studies were cited for Victoza. Existing human studies showed Victoza significantly delayed gastric emptying, but these were not cited by Sanofi.

Novo Nordisk believed that for Lyxumia to reliably be labelled as a 'once-daily prandial' agent, it was necessary for it to reduce absolute prandial glucose levels across all meals in the day. Novo Nordisk alleged that the available evidence could not support the PPG lowering effect of Lyxumia throughout the whole day. Sanofi refused to provide data requested by Novo Nordisk in order to assess whether Lyxumia demonstrated this efficacy. Sanofi had provided modified data.

Novo Nordisk therefore alleged that the claim 'The only once-daily prandial GLP-1 receptor agonist' was misleading as it implied greater efficacy than supported in the evidence and disparaged Victoza. Breach of Clauses 7.2, 7.10 and 8.1 were alleged.

RESPONSE

Sanofi noted that GLP-1 receptor agonists were used in the treatment of type 2 diabetes and activated the endogenous GLP-1 receptor. Once activated, this receptor acted on multiple pathways to enhance the action of endogenous insulin, regulated endogenous glucagon secretion and delayed gastric emptying. These factors all served to reduce circulating glucose concentrations and improve the hyperglycaemia that was characteristic of diabetes. Lyxumia and Victoza were the only once-daily GLP-1 receptor agonists licensed for use in the UK (the other GLP-1 receptor agonists were used twice daily or once weekly).

The degree to which each pathway was activated had been shown to depend upon the pharmacodynamic profile of the individual agents. The reference to 'prandial' was made to distinguish Lyxumia from Victoza on the basis that a clear distinction was seen between the two in terms of their mode of action which reflected different pharmacokinetic profiles and pharmacodynamic effects. This was clearly reported in the scientific literature, and confirmed by different requirements for posology for the products. There was a specific requirement for Lyxumia to be given at meal times, as would be expected for a prandial agent; this was captured in Section 4.2 of the Lyxumia SPC. No such requirement existed for Victoza which was to be given 'at any time, independent of meals' as per Section 4.2 of its SPC.

Sanofi noted that Novo Nordisk had: challenged the definition of 'prandial'; purported that Victoza had a prandial effect and that Lyxumia could not therefore be termed 'the only once-daily prandial' agent; stated that Victoza had an effect on gastric emptying and contended that Lyxumia failed to maintain a prandial effect throughout the entire day.

Sanofi submitted that Novo Nordisk had not put forward sufficient evidence to support its allegations. Sanofi was confident that the information presented was a balanced and accurate representation of the up-to-date evidence base, and that the materials at issue complied with the Code.

Sanofi submitted that the treatment of diabetes needed to be considered to understand the term 'prandial' within context. One of the common methods of treating long-standing type 2 diabetes was to administer basal (long-acting) insulin, which met the background need for insulin matched to the body's own production of glucose, which happened at a constant rate. Basal insulin, with a constant level of activity, could stabilise the background blood glucose levels during periods of fasting, but could not control the peak in blood glucose that occurred with meals. Other prandial agents, such as fast-acting or prandial insulin, were administered in conjunction with meals and were required to account for these post-prandial peaks. Lyxumia ultimately had the same effect as prandial insulin – it accounted for the peaks in blood glucose that occurred after meals and was licensed for the treatment of type 2 diabetes.

Contrary to Novo Nordisk's statement, Sanofi had not introduced the term 'prandial' to describe Lyxumia. The term prandial was already well known – a 'prandial insulin' was to be taken with a meal and reduced the post-prandial blood glucose peak. Clear clinical grounds existed that already saw GLP-1 receptor agonists categorised as 'prandial' – given with meals to affect the post-prandial blood glucose related to a meal, or 'non-prandial' – given irrespective of meals to affect primarily the fasting blood glucose levels. Lyxumia was widely described as a 'prandial' GLP-1 receptor agonist in peer reviewed scientific literature. Sanofi submitted that describing Lyxumia in this way was a fair representation of current scientific understanding.

Meier (2012) summarised existing knowledge and made a clear distinction between two modes of action of GLP-1 receptor agonists based on the predominant effect:

- Short-acting GLP-1 receptor agonists (such as exenatide and Lyxumia) predominantly lower post-prandial glucose levels and insulin concentrations via retardation of gastric emptying. (This resulted in a reduced rate of glucose release from the stomach and a direct reduction on the rise in glucose related to meals).
- Long-acting GLP-1 receptor agonists (such as exenatide LAR (long-acting release) and Victoza) predominantly lowered fasting blood glucose levels through stimulation of insulin secretion and reduction of glucagon levels.

Marathe *et al* (2013) described the relationship between gastric emptying, post-prandial glycaemia and incretin hormones. The authors summarised the current understanding that some GLP-1 receptor agonists 'slow gastric emptying and that [this effect] is, at least in some cases, an important mechanism by which they lower post-prandial glucose excursions'. Further, that due to differing half-lives GLP-1 receptor agonists 'vary in the magnitude of their effects on pre- versus post-prandial glycaemia'.

Marathe *et al* compared the two GLP-1 receptor agonists with a relatively short duration of action (Lyxumia and exenatide) with those of a longer duration of action (Victoza and exenatide LAR). They highlighted the observations from studies of type 2 diabetics that the short-acting agents – exenatide and Lyxumia – acted by lowering post-prandial glucose excursion through a predominant effect of sustained inhibition of gastric emptying. Conversely, the longer-acting medicines – exenatide LAR and Victoza – acted to lower fasting (pre-prandial) glucose levels through a predominant effect on the insulin/glucagon hormonal axes. The authors concluded that the short-acting agents – Lyxumia included – had a prolonged effect on post-prandial hyperglycaemia that was not demonstrated with the long-acting agents (including Victoza). The authors clearly differentiated the two categories of GLP-1 receptor agonists.

Fineman *et al* (2012) similarly reviewed the clinical effects of the GLP-1 receptor agonists and made the same distinction between the two groups, based on pharmacokinetic exposure – intermittent (from short-acting GLP-1 receptor agonists) and continuous (from long-acting receptor agonists). The authors made the same conclusions as Marathe *et al*, in that there were two distinct classes of GLP-1 receptor agonists: those which predominantly affected post-prandial glucose reduction, and those which predominantly affected fasting blood glucose.

Horowitz *et al* (2013) reviewed the clinical evidence available for Lyxumia and recognised its relatively short half-life and short duration of action, its once-daily regimen, as well as its clinical effect primarily mediated through lowering the exaggerated post-prandial glucose excursion in type 2 diabetes. The authors concluded it to be a 'once-daily prandial GLP-1 receptor agonist'.

To summarise, this wide body of evidence consistently classified GLP-1 receptor agonists as prandial or non-prandial agents:

- Prandial GLP-1 receptor agonists had a shorter half-life. They strongly inhibited gastric emptying and prevented a post-prandial increase in blood glucose (ie after food). Lyxumia and fast-acting exenatide (which was, however, administered twice a day) acted in this way.
- Non-prandial GLP-1 receptor agonists had a longer half-life. Long-acting GLP-1 receptor agonists had a self-limiting inhibitive effect on gastric emptying and food resorption. Non-prandial GLP-1 receptor agonists (such as Victoza) primarily affected fasting blood glucose levels.

Further to the scientific observation and supporting the 'prandial' description of Lyxumia was the specific requirement that it be administered at meal times, as would be expected with any other prandial agent, for example a prandial insulin. This was in direct contrast to the requirements for Victoza; the SPC indicated that it could be administered at any time of the day and specifically stated that this needed to be independent of meal times. This explicitly acknowledged a fundamental difference between the two medicines – Lyxumia was 'prandial' both in mechanism of action and the requirements for meal time administration, Victoza was neither.

Sanofi submitted that to describe Lyxumia as a 'prandial' agent was therefore entirely in keeping with the available evidence and Novo Nordisk had not provided any argument as to why this reference should not be cited to substantiate Lyxumia as a 'prandial' GLP-1 receptor agonist. Sanofi used 'prandial' quite rightly to differentiate Lyxumia from Victoza but this was not in an attempt to mislead – it correctly reflected the current understanding of the GLP-1 receptor agonist class of medicines, and was intended to meet the required standards of the Code.

Novo Nordisk stated that the Victoza SPC and Kapitza *et al* both indicated that Victoza effectively reduced post-prandial glucose throughout the day. Whilst on the surface this was a factually correct statement, on deeper examination it was clear to Sanofi that this would not be sufficient to support an implied claim that Victoza was a 'prandial' GLP-1 receptor agonist (and thereby to invalidate the observation that Lyxumia was the only once-daily prandial GLP-1 receptor agonist).

The 'prandial' description of Lyxumia was based on the observations conclusively outlined above: that its predominant effect on glycaemic control was through a reduction in post-prandial glucose excursion – that was the rise in blood glucose above the fasting/baseline level that occurred after eating. This was in contrast to the action of Victoza which acted predominantly to reduce fasting glucose levels.

Kapitza *et al* compared the pharmacodynamics of Lyxumia and Victoza and examined the impact of 28 days' treatment with each agent in type 2 diabetics. The study primarily assessed the ability of each medicine to suppress the prandial glucose excursion that followed a standardised test meal. The study demonstrated that after 28 days' treatment with Lyxumia, the post-meal excursion of glucose above baseline levels was more than completely abolished, whereas with Victoza, a significant glucose excursion remained and a highly significant difference was confirmed between the two medicines (reduction in glucose excursion: -129% vs -41% respectively, $p < 0.0001$). The authors also demonstrated that Victoza had a significantly greater effect than Lyxumia in lowering fasting glucose levels, consistent with the different clinical attributes of these medicines.

Sanofi noted that Novo Nordisk maintained that the authors concluded that Victoza effectively reduced PPG. However, early in the discussion the authors stated that '... the PPG-lowering effects observed

with some GLP-1 receptor agonists (lixisenatide and exenatide, but not liraglutide) appear to be due primarily to slowing of gastric emptying' which supported a true difference between the two medicines. Although a small reduction in glucose excursion was reported with Victoza, it was acknowledged as not being the result of the predominant mode of action of Victoza. This was clearly insufficient to substantiate a claim that Victoza was a prandial GLP-1 receptor agonist in the same way that had been demonstrated for Lyxumia.

Furthermore, it was clear from the supporting evidence provided by Novo Nordisk as part of the inter-company dialogue, that rather than acting on post-prandial glucose excursions, the effect of Victoza was to reduce fasting/baseline blood glucose. Data provided by Novo Nordisk clearly demonstrated a reduction in fasting blood glucose levels of 2-3mmol/L in each of three different studies (0.7-2.4mmol/L in the SPC).

As a consequence of this decreased baseline blood glucose level, there was also a decrease in post-prandial glucose levels of the same magnitude (the SPC quoted 1.7-2.7mmol/L). It was clear that this post-prandial reduction was mediated through the reduction in the fasting glucose levels rather than through any specific reduction in post-prandial glucose excursion – the post-prandial reduction seen simply reflected a lowered baseline, not the reduction in post-prandial excursion as seen with Lyxumia (4.5-8.0mmol/L post-prandial fall, on a background of minimal change in baseline levels of 0.4-1.2mmol/L).

In conclusion, although this observation supported the wording in the Victoza SPC that both fasting and post-prandial hyperglycaemia were reduced, this wording could not be extended so far as to support a claim that Victoza was also a prandial agent. To do so would be akin to recognising that a basal insulin which reduced baseline/fasting blood glucose levels (such as insulin detemir or insulin glargine) could also be called a prandial agent – and Sanofi was sure that neither party would ever countenance such a suggestion.

As already discussed, the effect of Victoza on delaying gastric emptying was recognised as being only of minor impact and not the prominent mechanism through which it exerted a glucose lowering effect – the effects on the insulin/glucagon axis in lowering fasting plasma glucose was the predominant mode of action. This was in contrast to the effects of Lyxumia which acted predominantly to delay gastric emptying and abolish the post-prandial glucose excursion. This was important as the different methods of action were the main features that distinguished the medicines.

Novo Nordisk alleged that inconclusive evidence was cited when referring to the effects of Victoza on gastric emptying. This was an unexpected statement given that Sanofi had cited the Victoza SPC which stated 'the mechanism of blood glucose lowering also involves a minor delay in gastric emptying'. Beyond this observation, it was clear that this observation was substantiated by studies in humans

– the evidence cannot be claimed 'inconclusive':

- Juhl *et al* (2002) compared a single dose of Victoza with placebo in patients with type 2 diabetes and described only a 9% reduction/15 minute delay in gastric emptying.
- Degn *et al* (2004) performed a similar study and at the end of one week's treatment there was no detectable difference in the rate of gastric emptying between patients receiving Victoza and placebo, either at breakfast or at the evening meal.
- Flint *et al* (2011) performed a three week comparison between Victoza (0.6, 1.2 and 1.8mg/day) and placebo in patients with type 2 diabetes. Although no significant reduction in gastric emptying was seen in the lower and higher doses, a small but statistically significant reduction was seen with the middle dose. The authors, however, commented that their study was of too short a duration for the expected tolerance to the gastric emptying to have developed to allow the study to assess this parameter appropriately and thus questioned the relevance of this result.

In summary, the current balance of scientific information indicated that the gastric emptying effect of Victoza appeared to be a minor component of its mechanism of action, and one which was not sustained. Tolerance developed rapidly (within days to weeks) and this was clearly relevant to treating a long-term condition.

Sanofi submitted that with Novo Nordisk's suggestion that for Sanofi to claim that Lyxumia was a prandial agent, it should demonstrate a lowering PPG level consistently throughout the day had no basis in science nor precedent – the fact that Lyxumia abolished the meal time glucose excursion defined its prandial mechanism of action, not the number of meals that this remained effective for after a dose was given. This effect did not need to be equally marked after all meals, or even to persist for all three meals in a day after a single dose. Novo Nordisk would agree that prandial insulin, for example, was likely to be effective only for the meal in relation to which it was administered.

That stated, however, Sanofi had provided evidence during inter-company dialogue to support the fact that there was significant reduction in the post-meal glucose excursion after each of three meals in the day after a morning dose of Lyxumia. To substantiate the fact did not require 'the full data analysis' referred to by Novo Nordisk. Furthermore, Lorenz *et al* (2012) showed that compared with placebo, the reduction in post-prandial exposure to glucose was significantly reduced by Lyxumia, given once in the morning, after three standardised test meals throughout the day (breakfast, lunch, dinner).

In summary, the prevailing scientific opinion and evidence classed GLP-1 receptor agonists as prandial or non-prandial according to their dominant mode of action. Lyxumia had a post-prandial action and was clearly classed as a prandial GLP-1 receptor agonist; Victoza clearly had a fasting mechanism of action and was classed as a non-prandial GLP-1

receptor agonist. Beyond this, a direct comparison by randomised clinical trial had demonstrated that Lyxumia completely abolished the post-prandial glucose excursion after a test meal, demonstrating a highly significant advantage over Victoza which had only a minor impact on the same parameter. Furthermore, randomised clinical trials showed that the post-prandial effect of Lyxumia was maintained throughout the day.

Sanofi thus denied a breach of Clauses 7.2, 7.10 and 8.1.

PANEL RULING

The Panel noted that the claim at issue was that Lyxumia was 'The only once-daily prandial GLP-1 receptor agonist'. The Panel noted that health professionals would be familiar with the term 'prandial' but considered that GLP-1 receptor agonists were not commonly described as such. The Panel disagreed with Sanofi's submission that Lyxumia was widely described in the literature as a 'prandial GLP-1 receptor agonist'. The only paper submitted by the parties to describe Lyxumia in this way was Horowitz *et al* which was published in 2013. Under 'Acknowledgements' at the end of the paper it was stated that Sanofi had been involved in the production of the paper and had had the opportunity to review the paper for scientific accuracy before the paper was peer reviewed. It was not stated whether the company had reviewed the paper. The authors cited the approval of Lyxumia by the European Medicines Agency in February 2013 and so in that regard the Panel queried whether the paper had been published before the mailer and the leavepiece had been approved (7 and 5 February respectively). In the Panel's view, health professionals would not be familiar with the description of a GLP-1 receptor agonist as a 'prandial GLP-1 receptor agonist'.

The Panel noted that apart from Horowitz *et al*, authors only described GLP-1 receptor agonists as short- or long-acting agents. Short-acting GLP-1 receptor agonists, eg Lyxumia, produced a modest reduction in fasting blood glucose levels and a strong reduction in post-prandial glucose levels. Conversely, long-acting GLP-1 receptor agonists, eg Victoza, produced a strong reduction in fasting blood glucose levels and a modest reduction in post-prandial glucose levels. Thus both short- and long-acting GLP-1 receptor agonists affected fasting and post-prandial blood glucose levels but each had a greater effect on one or the other.

The Panel noted that Lyxumia and Victoza were both once-daily medicines. Therefore the claim that Lyxumia was the only once-daily prandial GLP-1 receptor agonist implied that Victoza had no prandial action at all. The Panel accepted that in a 28 day study, Lyxumia had been shown to decrease post-prandial glucose levels. Although the after breakfast (standardised test meal) data showed an advantage for Lyxumia compared to Victoza nonetheless, Victoza did decrease post-prandial glucose levels from those which were seen at baseline (Kapitza *et al*). The Panel further noted that in Section 5.1 of the Victoza SPC it was stated that '[Victoza] has 24 hour duration of action and improves glycaemic

control by lowering fasting and post-prandial blood glucose in patients with type 2 diabetes mellitus'. The comparable statement in the Lyxumia SPC read 'When administered once daily, [Lyxumia] improves glycaemic control through the immediate and sustained effects of lowering both post-prandial and fasting glucose concentrations in patients with type 2 diabetes'.

The Panel noted that Sanofi had submitted that there was not enough data to support a claim that Victoza was a prandial agent. In the Panel's view however, this was not the issue; the claim at issue was about what Lyxumia was and by implication, what Victoza was not. The Panel considered that as the claim stated that Lyxumia was the only once-daily prandial GLP-1 receptor agonist it implied that the only other once-daily GLP-1 receptor agonist ie Victoza had no prandial effect at all which was not so. The Panel considered that readers would be unfamiliar with the term 'prandial GLP-1 receptor agonist'. The Panel considered that the claim was misleading and exaggerated and ruled a breach of Clause 7.2 and 7.10. The Panel further considered that the claim disparaged Victoza by implying that it had no prandial action. A breach of Clause 8.1 was ruled. These rulings were appealed by Sanofi.

APPEAL FROM SANOFI

Sanofi submitted that the Panel had recognised that clear differences existed between the two once-daily GLP-1 receptor agonists – ie that Lyxumia was a short-acting agent and Victoza a long-acting agent, and that the different durations of action directly related to the presence/absence (respectively) of an important effect on gastric emptying after a meal.

Sanofi submitted that 'prandial' had been used to describe the short-acting GLP-1 agonists reflecting this mechanism of action. The Panel however ruled that this claim was inappropriate on the basis that: 'prandial' was not widely applied to describe GLP-1 agonists; health professionals would be unfamiliar with the term, and Victoza also reduced post-prandial glucose and Lyxumia could not, therefore, be the only prandial GLP-1 agonist.

Sanofi submitted that short-acting GLP-1 receptor agonists had been described as 'prandial' in the literature since at least 2010. Further references were provided to demonstrate the description of 'prandial exenatide' and Lyxumia as a 'prandial GLP-1' (Elkinson and Keating 2013, Pinkney *et al* 2013). Sanofi further submitted that 'prandial' was by definition 'related to meals' and this term would be readily understood, especially by health practitioners who cared for people with diabetes. It was widely used to describe both the increased blood glucose levels related to meals, and as a descriptor for medicine classes – prandial glucose regulators ('glinides') and prandial (rapid-acting) insulins in particular – each taken at meal times to control the exaggerated post-prandial glucose excursion in type 2 diabetes. To conclude that health professionals would not recognise the term 'prandial GLP-1 receptor agonist' failed to appreciate the knowledge and experience of those to whom the material was directed.

Sanofi noted that the Panel acknowledged that Lyxumia was a short-acting agent and Victoza a long-acting agent, and that the different durations of action directly related to the presence or absence, respectively, of the important effect of delayed gastric emptying after a meal. The presence (or absence) of this meal-time effect conveyed the different pattern of blood glucose control that was seen with each agent – ie the predominant effect of Lyxumia to reduce the post-prandial glucose excursion and that of Victoza to reduce fasting (or baseline) blood glucose levels.

Sanofi submitted that the Panel identified a statement within the Victoza SPC that Victoza reduced post-prandial glucose, but had incorrectly assumed that this equated to a specific prandial ('meal-related') effect. The Panel had failed to appreciate that reducing absolute post-prandial glucose levels was different to the specific prandial effect of abolishing or significantly reducing the post-meal increase – the 'glucose excursion' – above baseline levels. A reduction in absolute post-prandial glucose levels could be achieved in the absence of any specific prandial effect through the reduction in baseline (pre-meal) glucose levels alone. An identical increase in post-meal blood glucose, but on the background of a lowered baseline, resulted in a reduced post-prandial glucose value, despite the size of the post-meal increase being unchanged. A reduced prandial glucose excursion required a meaningful reduction in the rise of post-meal glucose levels relative to pre-meal values, as was seen with Lyxumia. Kapitza *et al* showed that Lyxumia completely abolished the post-prandial glucose excursion and was significantly different to Victoza in this respect; this confirmed the unique prandial action of Lyxumia and justified the description of 'the only once-daily prandial GLP-1'.

Sanofi further submitted that 'prandial' could be applied to the posology of Lyxumia. It was the only once-daily GLP-1 agonist required to be given at meal times – the SPC directed 'within the hour prior to the first meal of the day or the evening meal'. Conversely, the SPC for Victoza indicated that it was 'administered once daily at any time, independent of meals'. This was a clear point of differentiation and in itself justified the description 'only once-daily prandial GLP-1 agonist'. In summary, Sanofi submitted that in light of the evidence currently available the description of Lyxumia as 'the only once-daily prandial GLP-1 agonist' was not misleading or exaggerated, and by implication did not disparage Victoza.

COMMENTS FROM NOVO NORDISK

Novo Nordisk stated that a health professional's interpretation of the word 'prandial' was the key consideration.

Sanofi appropriately stated that 'prandial' by definition related to meals and correctly linked the health professional's understanding of the word prandial with the individual's experience of using prandial glucose regulators ('glinides') and prandial rapid-acting insulins. Glinides stimulated pancreatic

beta cells to produce more insulin in a glucose independent manner, while rapid-acting insulin served as simple replacement for inadequate insulin secretion during periods of high blood glucose concentration – eg 'prandial periods'. Therefore every health professional would know that both classes of medicine worked in a rapid-acting, glucose independent manner. These agents covered the period immediately after the dose and needed to be administered before every main meal in order to provide full daily prandial coverage. This was also reflected in the SPCs for medicines in these two classes.

Novo Nordisk therefore agreed with Sanofi that this was exactly the understanding (linked to use of glinides and rapid-acting insulins) a health professional would have when presented with the terms 'prandial' and 'basal'.

Novo Nordisk noted that in contrast, GLP-1 receptor agonists worked in a glucose dependent manner, at periods when blood glucose concentration was high (eg in prandial periods after meals), to stimulate pancreatic beta cells to produce more insulin. This had been confirmed by the low rate of hypoglycaemia in clinical trials for medicines in this class. Therefore all GLP-1 receptor agonists including long-acting agents had a prandial effect as supported by the scientific evidence and reflected in the Victoza and once weekly exenatide (Bydureon) SPCs. Novo Nordisk was not aware of any original scientific research to prove the opposite nor had Sanofi provided this evidence.

The Panel correctly noted that apart from Horowitz *et al*, the authors of the other three publications submitted by Sanofi only described GLP-1 receptor agonists as short- or long-acting. Of the two references provided by Sanofi with its appeal, Novo Nordisk noted that Elkinson and Keating was a very recently published R&D insight report. The publication was authored by employees from the Adis R&D Insight database, who described the database as being 'An exhaustive compilation of drug programs worldwide, with drug profiles updated daily using information from company contacts, press releases, international conferences, company websites, and medical journals'. Consequently the report was subject to bias towards Sanofi. Novo Nordisk noted that Pinkney *et al*, used the word 'prandial' just once in the abstract to describe the dosing of exenatide twice daily ie in relation to meals, rather than Sanofi's interpretation that the word 'prandial' described the comparative effects of either treatment of reducing post-prandial glucose. The authors neither suggested a lack of post-prandial glucose control with Victoza nor made a distinction between the two products based on post-prandial glucose lowering efficacy.

As a result of the above, Novo Nordisk alleged that these two publications did not provide convincing evidence that prandial could be widely applied to describe GLP-1 receptor agonists. Novo Nordisk thus agreed with the Panel that health professionals would be unfamiliar with the term 'prandial GLP-1 receptor agonist'.

Novo Nordisk noted that as provided in inter-company dialogue, the scientific evidence showed that Victoza lowered post-prandial glucose over all three meals of the day. Therefore, Novo Nordisk alleged that health professionals could only conclude from the scientific evidence that Victoza had some prandial action. The same applied to Bydureon (Kim *et al* 2007). Making the distinction within the GLP-1 receptor agonist class based on the word 'prandial' was misleading, as all agents acted with a prandial effect due to their mechanism of action.

Novo Nordisk stated that in Kapitza *et al*, which compared the post-prandial glucose lowering effect of short- and long-acting GLP-1 receptor agonists after the first meal post-injection, the short-acting agent was expected to provide better efficacy over this first meal period. As correctly noted by the Panel this did not mean that a long-acting compound (Victoza) showed no prandial effect at all after breakfast. Additionally, Novo Nordisk alleged that the claim 'The only once-daily prandial GLP-1 receptor agonist' implied post-prandial glucose efficacy across 24 hours. Kapitza *et al* concluded that Victoza provided better post-prandial glucose control than Lyxumia beyond the morning meal. Novo Nordisk was disappointed with the lack of transparency and proper scientific dialogue from Sanofi with regard to the refusal to share the data from Kapitza *et al* needed to establish medicine profiles beyond the morning meal.

In inter-company dialogue Sanofi presented an analysis of the post-prandial glucose excursions dividing the post-prandial period into the prior fasting plasma glucose level and the additional increment of glucose as a specific 'prandial glucose excursions'. Novo Nordisk alleged that this had no grounding in clinical practice whereby post-prandial glucose was measured as an absolute level.

Novo Nordisk emphasised that fasting blood glucose concentration was an important aspect in the management of a patient's blood glucose profile, and should not be eliminated from any analysis of the data. Novo Nordisk alleged that the improved fasting blood glucose lowering efficacy of Victoza vs Lyxumia was the consequence of a longer half-life as recognised by Kapitza *et al*, and not caused by any mechanism of action specific to Victoza as a 'non-prandial' agent. Any glucose level above 7mmol/l was recognised as abnormally raised blood glucose, a sign of diabetes. Therefore the glucose dependent reductions in plasma glucose seen with Victoza in Kapitza *et al*, were clinically relevant to both the post-prandial and fasting plasma glucose periods. Graphical manipulations of the post-meal data vs baseline, served no other purpose than to disparage the efficacy of Victoza. Novo Nordisk noted that if the same graphical manipulation was applied to the 24 hour blood glucose profile for Lyxumia, it might be concluded that Lyxumia increased the blood glucose levels after the second meal post-injection (lunch). Novo Nordisk believed that Sanofi would strongly object to this conclusion.

In addition, Novo Nordisk alleged that it was clear from Kapitza *et al* that Victoza also decreased

prandial glucose 'excursions' – unfortunately Kapitza *et al*, failed to report whether Victoza decreased prandial glucose 'excursions' from baseline level. In addition, Novo Nordisk was further disappointed that Sanofi presented prandial glucose 'excursions' discussions to the Panel but failed to mention Flint *et al* who clearly demonstrated that Victoza significantly decreased post-prandial glucose 'excursions'.

Novo Nordisk agreed with the Panel that the claim in question implied that Victoza had no prandial effects at all, which was incorrect.

Novo Nordisk alleged that Sanofi had attempted to introduce an artificial distinction in the GLP-1 receptor agonist class by categorising them into 'prandial' and basal (similar to insulin). As suggested by Sanofi, Victoza reduced baseline blood glucose levels and not 'prandial' blood glucose levels as defined by health professionals' experience with glinides and rapid-acting insulin.

It appeared that Sanofi had compared the action of Victoza to long-acting (basal) insulins which provided support during the post-absorptive state and covered 'basal' insulin needs. Novo Nordisk reiterated that Victoza reacted differently to basal insulin and specifically acted during periods of high blood glucose, especially during post-prandial periods.

Novo Nordisk disagreed with Sanofi's statement that the Panel had acknowledged the difference between short- and long-acting GLP- receptor agonists and that the different durations of action related to the presence or absence of gastric emptying. In its ruling, the Panel stated that it recognised the different pharmacokinetic profiles of the two products, but did not relate this to the presence or absence of gastric emptying to support the duration of effect. Any assertion of an 'absence' of a gastric emptying effect in relation to Victoza was factually incorrect – various clinical studies and the Victoza SPC described an effect of Victoza on gastric emptying. Novo Nordisk emphasised that the effect of Lyxumia on gastric emptying had been studied just in the first meal post-injection and there was no indication of what the effect would be to subsequent meals during the day.

Nevertheless, Novo Nordisk stated that slowing of gastric emptying was just one of the less well explored potential mechanisms of action attributed to GLP-1 receptor agonists that might play a small role in the overall efficacy of all of them.

Novo Nordisk alleged that this argument was based on inconclusive and unfounded evidence and should not be used as a basis to make a misleading claim.

Novo Nordisk noted that in its appeal, Sanofi used another potential definition of the word 'prandial' in relation to its required dosage at meal times. This definition was very different to its previous definition: 'prandial had been used as the descriptive term for the short-acting-GLP-1 agonists reflecting this mechanism of action'. This showed that Sanofi had exploited the word 'prandial' and used it in an ambiguous way in order to make a misleading

claim. Nevertheless, even if the time of medicine administration was considered, Victoza in this context might still be considered as 'prandial' as it could be given at any time, including meal times.

Based on the above, Novo Nordisk supported the Panel's rulings of a breach of Clauses 7.2, 7.10 and 8.1 of the Code.

APPEAL BOARD RULING

The Appeal Board referred to Section 5.1, Pharmacodynamic properties, of the Lyxumia SPC and noted that under a heading of 'Mechanism of action' it was stated that:

'Lixisenatide is a selective GLP-1 receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells.

Lixisenatide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in intracellular cyclic adenosine monophosphate (cAMP). Lixisenatide stimulates insulin secretion when blood glucose is increased but not at normoglycaemia, which limits the risk of hypoglycaemia. In parallel, glucagon secretion is suppressed. In case of hypoglycaemia, the rescue mechanism of glucagon secretion is preserved.

Lixisenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.'

The Appeal Board thus noted that only the last sentence referred to what Sanofi had referred to as the predominant mechanism of action of Lyxumia; delay in gastric emptying.

The Appeal Board noted Sanofi's submission that prandial meant 'pertaining to a meal' and that Lyxumia fitted this description in at least two ways – ie its predominant mechanism of action and its requirement to be given once daily, within the hour prior to either the first meal of the day or the evening meal. The Appeal Board noted that Lyxumia lowered both fasting and post-prandial glucose concentrations. Victoza also had a dual mechanism of action. It was given once daily at any time, independent of meals. The Appeal Board did not consider that the term 'prandial' in the claim 'The only once-daily prandial GLP-1 receptor agonist' could be used to distinguish Lyxumia from Victoza. 'Prandial' in the claim at issue appeared to have a different meaning compared with when it was currently more usually used to describe insulins or glucose regulators (glinides). In the Appeal Board's view, health professionals would thus not understand what Sanofi meant by a 'prandial GLP-1 receptor agonist'. The Appeal Board noted that GLP-1 receptor agonists were more usually, and currently, differentiated in the literature according to length of action ie long-acting (Victoza) and short-acting (Lyxumia). The Appeal Board considered that the claim that Lyxumia was 'The only once-daily

prandial GLP-1 receptor agonist' was misleading and exaggerated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The Appeal Board further considered that the claim disparaged Victoza as it implied that Victoza had no prandial action which was not so. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1. The appeal was thus unsuccessful.

2 Claim 'A positive addition can make all the difference'

This claim appeared in the leavepiece and on the exhibition stand.

COMPLAINT

Novo Nordisk alleged that the claim over-promised on the benefits that Lyxumia offered. No treatment could make all the difference and 'all' implied a greater improvement to a person with type 2 diabetes than simply a post-prandial glucose lowering effect over one meal in the day. Breaches of Clauses 7.2 and 7.10 were alleged.

RESPONSE

Sanofi submitted that this claim was simple, clear and unambiguous, did not imply any benefit beyond that of adding any additional anti-hyperglycaemic agent at the point at which additional therapy was required, and above all did not imply that Lyxumia (or any medicine) would deliver any particular effect – only that there was the potential for benefit to occur. It was a stimulus to the reader to consider additional therapy for patients with type 2 diabetes when this was needed. To direct that choice towards Lyxumia as being the sought-after positive addition was the intent of the rest of the item, not this individual claim.

Sanofi submitted that the claim related broadly to the treatment of diabetes and not directly to Lyxumia (although Sanofi recognised, of course, that it was promotional material for Lyxumia). The claim did not refer to any expected effect, positive or negative. Critically, if that was the implication, the use of the conditional 'can' (as opposed to the direct 'will' or 'does') made it clear that not every patient would be so affected. Taking all these factors into consideration, Sanofi did not consider that the claim was misleading or all-embracing.

Sanofi noted that Novo Nordisk had alleged that the claim attempted to portray an all-encompassing effect of Lyxumia and referred to benefits beyond glycaemic control. Sanofi failed to see how this could be so. There was no reference to or even suggestion of any benefit to 'blood pressure, lipid control, neuropathy and other complications', and to suggest such an association was at odds with the nature of the item.

Sanofi concluded that the claim was clear, unambiguous and invited readers to consider that when additional therapy was required for patients with type 2 diabetes, additional therapy should be considered. Sanofi expected that the typical reader

would reach this same conclusion, and failed to see how any other interpretation would be arrived at. Sanofi denied a breach of Clauses 7.2 or 7.10.

PANEL RULING

The Panel disagreed with Sanofi's submission that the claim 'A positive addition can make all the difference' related broadly to the treatment of diabetes and not directly to Lyxumia. The claim was an integral part of Lyxumia promotional material; it appeared adjacent to a picture of the Lyxumia pre-filled pen. 'Positive addition' was written in a font the same colour as the pen. In the Panel's view readers would associate the broad, unqualified claim with Lyxumia.

The Panel considered that as the claim was unqualified it was impossible to know what it meant with regard to Lyxumia treatment; readers would interpret it in their own way. In that regard the Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled. The Panel further considered that the broad claim was exaggerated and a breach of Clause 7.10 was ruled.

3 Claim 'Strong evidence supporting the use of Lyxumia as add-on to basal insulin'

This claim appeared in the leavepiece, the mailer and on the exhibition stand and was referenced to Rosenstock *et al* (2012) and Riddle *et al* (2012).

COMPLAINT

Novo Nordisk stated that while both Rosenstock *et al* and Riddle *et al* were designed to be of sufficient quality, the published results of each randomised clinical trial demonstrated insubstantial efficacy to support the claim 'strong'. Novo Nordisk noted that the European Medicines Agency (EMA) appeared to hold a similar opinion on this point, as mentioned by Sanofi in its letter of 3 April 2013. Novo Nordisk alleged a breach of Clause 7.10.

RESPONSE

Sanofi submitted that it had claimed 'Strong evidence to support benefit', not 'Evidence of strong benefit'.

To provide an overview of the evidence that supported the use of Lyxumia with basal insulin, Sanofi conducted three randomised controlled trials

in this clinical setting (GetGoal-L, GetGoal-L Asia, GetGoal-Duo1) each adequately powered and with a sufficient number of patients to draw a meaningful conclusion. This programme provided the greatest Phase III trial reported experience of a GLP-1 receptor agonist used in combination with basal insulin. In itself, one well conducted, randomised trial took a high position in any ranking of evidence (second only to systematic review in the Oxford CBEM Level of Evidence scale). It was difficult to consider three well-conducted randomized clinical trials showing similar results as anything but strong.

Although Novo Nordisk continued to make its point over the strength of the evidence, the EMA had clearly recognised that this was adequate to support a licensed indication for the use of Lyxumia in combination with basal insulin.

Sanofi submitted that the evidence base for Lyxumia in combination with basal insulin was sufficiently robust to be considered 'strong'; further, the evidence itself was of sufficient strength to support the granting of a relevant marketing authorization to allow its use in this way. Sanofi was confident that this was reflected in the nature of the marketing authorization. The company denied a breach of Clause 7.10.

PANEL RULING

The Panel noted that Lyxumia was indicated for the treatment of type 2 diabetes to achieve glycaemic control in combination with an existing treatment regimen that included insulin, where the existing medicinal therapy, together with exercise and diet, had failed to provide adequate glycaemic control. In that regard the Panel noted that the company would have had to submit evidence to the regulatory authorities that such use of Lyxumia was well tolerated and effective. The Panel considered that to describe such evidence as 'strong' implied some special merit – all evidence provided for the grant of any marketing authorization had to be robust. In that regard the Panel considered that the claim exaggerated the strength of the data and it ruled a breach of Clause 7.10.

Complaint received	29 April 2013
Case completed	7 August 2013

ANONYMOUS v UCB

Declaration of support to patient organisation

An anonymous, non-contactable complainant, described as a neurologist, complained about two aspects of the UK website for UCB Pharma.

The detailed response from UCB is given below.

The complainant alleged that UCB had flouted the requirement to declare payments or benefits in kind made to UK patient organisations. The complainant referred to the company's support of a health board (via a patient organisation) by providing a specialist nurse to train health professionals. No declaration of this support was included on the company's website.

The Panel noted UCB's submission that the activity at issue was a joint working project and it had publicly declared its involvement in that project as required by the Code. UCB had submitted that the amounts it had paid to the patient group in relation to that project were fee for service payments. The Panel considered that these payments should have been declared in accordance with the Code. There was no declaration of these payments on the company's website. However, the company had been asked to respond in relation to the declaration of payments of financial support as opposed to fees for service and so the Panel ruled no breach of the Code in that regard.

The Code required that an executive summary of joint working agreements be made publicly available before arrangements were implemented. UCB had published an executive summary of the agreement on its website; no breach of the Code was ruled in this regard.

The complainant understood that the UCB website should be approved internally and re-approved every two years but noted that in May 2013, the website continued to carry an approval date of March 2011.

The Panel noted UCB's explanation regarding the dates and codes which appeared at the bottom of its corporate website pages. The Panel noted that although the website commissioning date of March 2011 appeared in the bottom left-hand corner of every webpage, the significance of the date was not explained. However, in the right-hand corner of every page, and in the same size font, the date of the last update was clearly stated. The Panel did not consider that the complainant had demonstrated that relevant pages of the website had not been recertified as required by the Code. No breaches of the Code were ruled.

An anonymous, non-contactable complainant, described as a neurologist, complained about two aspects of the UK website for UCB Pharma Ltd (www.ucbpharma.co.uk).

1 Failure to declare support for patient organisation

COMPLAINT

UCB emphasised that it was committed to the highest standards of corporate conduct and maintained a compliance programme in accordance with industry standards. As a member of the ABPI, UCB was committed to operate in a professional, ethical and transparent manner and abide by the Code.

UCB noted that Clause 23.7 dealt with the public declaration requirements in relation to working with patient organisations.

The support of the health board (via the patient group) referred to in the complaint related to a joint working project, which was described in more detail below. Accordingly, Clause 18.5 which dealt with joint working between one or more pharmaceutical companies and health authorities and trusts was relevant.

The joint working project at issue was between the patient group, health board, another named pharmaceutical company and UCB. The ultimate beneficiaries of the project would be people with epilepsy through services provided by the health board. The objectives of the project were to improve and develop the provision of such services by the health board.

UCB stated that in accordance with Clause 18.5, the parties entered into a written joint working agreement to record the roles and responsibilities of each of the parties and other terms governing the implementation of the project. UCB offered to provide a copy of the joint working agreement if necessary but noted that it was subject to confidentiality restrictions and required consent from all the parties involved.

In addition, in accordance with the requirements of Clause 18.5, an executive summary of the joint working project was made publicly available by UCB shortly afterwards on its UK website under the 'Partners' webpage. Similarly, an executive summary was also made publicly available by the other named pharmaceutical company, on its website under 'Joint Working'.

As this was a joint working project and therefore governed by Clause 18.5, UCB submitted that it had faithfully publicly declared its involvement in it as required by the Code, and that the website disclosure met the requirements of Clause 18.5.

UCB strongly believed that it was not in breach of the Code and that the complainant appeared to have

misinterpreted UCB's corporate website and the location of its public declarations and disclosures.

* * * * *

On receipt of UCB's response in which it submitted that the activity at issue was a joint working project, the Authority invited any further comments that UCB wanted to make in relation to Clause 18.5. The company stated that it did not wish to make any further comment.

* * * * *

In response to a request from the Panel for further information, UCB provided details of the amounts paid to the patient group in relation to the joint working project. UCB submitted that these were fee for service payments in response to individual invoices and not donations.

UCB stated that, in summary, the patient group's responsibilities as a joint working partner under the joint working agreement were to:

- provide an epilepsy nurse specialist to deliver training
- be a direct link to government
- manage PR
- publish results
- provide secretariat support
- prepare training materials
- liaise with professional bodies and CPD accreditation
- monitor and audit quality objectives and key performance indicators
- produce high quality evidence-based patient information resources.

UCB provided a copy of the joint working agreement and accompanying business case which detailed the patient group's role within and contribution to the project and UCB's financial obligation to the patient

PANEL RULING

The Panel noted that Clause 23.7 stated that each company must make publicly available, at a national or European level, a list of patient organisations to which it provided financial support and/or significant indirect/non-financial support, which must include a description of the nature of the support that was sufficiently complete to enable the average reader to form an understanding of the significance of the support. The list of organisations being given support must be updated at least once a year. The published information must include the monetary value of financial support and of invoiced costs. For significant non-financial support that could not be assigned a meaningful monetary value, the published information must describe clearly the non-monetary value that the organisation received.

The Panel noted UCB's submission that Clause 23.7 dealt with the public declaration requirements in relation to working with patient organisations but that as the support of the health board (via a patient group) referred to in the complaint related to a joint working project, it was governed by Clause 18.5 and

UCB had publicly declared its involvement in that project as required by the Code.

The Panel noted that joint working projects were originally expected to be between the industry and the NHS. It noted that the Department of Health defined joint working as situations where, for the benefit of patients, one or more pharmaceutical companies and the NHS pooled skills, experience and/or resources for the joint development and implementation of patient centred projects and shared a commitment to successful delivery. There was no reason, however, why patient organisations should not also be involved. In joint working projects the wording of Clause 18.5 referred to joint working between pharmaceutical companies and health authorities and trusts and the like which would include patient organisations. In the Panel's view companies would have to consider the requirements of both Clause 18.5 and Clause 23 in relation to joint working projects which involved patient organisations. Thus if joint working involved payments from a pharmaceutical company to a patient organisation such as a donation or fee for service, the payments should be declared in accordance with Clause 23. The Panel noted that Clause 23 did not include any exemptions for payments made to patient organisations in relation to joint working.

The Panel noted that the joint working agreement provided by UCB stated that the other named pharmaceutical company and UCB should comply with the requirements of the Code and their own internal codes of practice to ensure that all involvement with the patient group, including the amount of funding and the percentage that such funding represented to the patient group, would be declared on the companies' corporate websites. The patient group gave its approval to such disclosure.

UCB had submitted that the amounts it had paid to the patient group in relation to the joint working project were fee for service payments. The Panel considered that these payments should have been declared in accordance with Clause 23.8. There was no declaration of these payments on the company's website. The company had not been asked to respond in relation to Clause 23.8 and so the Panel could make no ruling in that regard. The company had been asked to respond in relation to Clause 23.7. As this covered the declaration of payments of financial support as opposed to fees for service, the Panel ruled no breach of Clause 23.7; the payments in question were not covered by that clause.

Clause 18.5 required, *inter alia*, that an executive summary of joint working agreements be made publicly available before arrangements were implemented. Given that the complainant referred only to declaration of involvement the Panel only considered the joint working project in relation to this narrow aspect.

The Panel noted UCB's submission that the joint working project between the patient group, the health board, other named pharmaceutical company and UCB aimed to improve and develop the provision of services by the health board for epilepsy

patients. The Panel noted that the parties had entered into a written agreement which recorded the roles and responsibilities of the parties and the financial arrangements as well as other terms and conditions governing the project's implementation. In addition, UCB had published on its website an executive summary of the joint working agreement in accordance with Clause 18.5. Overall, the Panel considered that the public declaration of the joint working project met the requirements of Clause 18.5 and no breach of that clause was ruled.

2 Failure to re-approve website content

COMPLAINT

The complainant understood that the UCB website should be approved internally and re-approved every two years. The complainant noted, however, that in May 2013 the website continued to carry an approval date of March 2011.

When writing to UCB, the Authority asked it to respond in relation to Clauses 14.1 and 14.5 of the Code.

RESPONSE

UCB noted that Clause 14 dealt with the certification requirements for certain materials, in particular promotional material (Clause 14.1), meetings involving travel outside the UK (Clause 14.2) and material expressly covered by Clause 14.3. Corporate websites *per se* did not require certification under the Code. However, where a particular webpage or information held on a corporate website contained material which fell within the scope of Clauses 14.1, 14.2 or 14.3, certification was required. UCB examined all information on its corporate website to ensure that it complied with the Code and to confirm whether or not certification under Clause 14 was required. If certification was required, then all necessary steps were taken to comply with the requirements of Clause 14 including Clause 14.5 with respect to re-certification.

The complaint related specifically to UCB's UK website. This was a functional corporate website which could be accessed by the public and contained general information about UCB's UK operations. In particular, it had separate webpages on 'Patients' (wherein UCB declared its support for patient organisations in the UK) and 'Partners' (wherein it had declared the joint working project described in Point 1 above).

In addition, the website contained information that would normally be expected to be made available to the public via a corporate website, including UCB's history, culture and values, information for job seekers, corporate social responsibility activities, research and development and a media room containing copies of UCB's latest press releases.

With regard to the dates which appeared at the bottom of each webpage, UCB explained that: the bottom right-hand side of each webpage had a reference date labelled 'Last update: ...'. The date

recorded here might differ for each webpage and indicated the last date on which that particular page was updated by UCB. The bottom, left-hand side of every webpage was the code and date '10MIS0004a/March 2011'. This described the original website commissioning internal reference number and date. The commissioning date, March 2011, was the same for all webpages because that was the date that UCB commissioned the corporate website as a whole, and therefore it would not change. The internal reference number did not indicate certification for the purposes of the Code.

UCB assumed that the complainant had referred to the website commissioning number and date and, as explained above, that particular reference number and date did not refer to any 'approval date' for Code purposes. UCB noted that press releases on its corporate website also carried their own individual reference numbers, which indicated that in accordance with the Code, these had been examined to ensure that they did not contravene it.

Currently, the only item and webpage on UCB's corporate website that required certification pursuant to Clause 14 was the executive summary of the joint working project referred to at Point 1 above. The executive summary was thus duly certified before it was uploaded. UCB stated that as evident from the dates shown at the bottom right-hand side 'Last update: 2013-04-08', that specific webpage was last updated on 8 April 2013 and, furthermore, the executive summary itself recorded the date of preparation at the bottom of that executive summary as March 2013 ('UK/12MIS0062a/Date of preparation March 2013'). It was this number and date which referred to certification.

Based on the above explanation of the dates on UCB's corporate website pages and the requirements of Clause 14, UCB submitted that it had complied with Clauses 14.1 and 14.3 and was not in breach, and that the complainant had misinterpreted the information contained on the footer of UCB's corporate webpages.

Finally, although UCB firmly believed it was not in breach of the Code for the reasons described above, following the resolution of this case, it would try to clarify its website in an effort to prevent any similar misinterpretation in the future.

PANEL RULING

The Panel noted that the complainant had not highlighted specific pages on the website but had made a general allegation that the website continued to carry an approval date of March 2011. The complainant understood that the website should have been approved internally and re-approved every two years.

The Panel noted that the Code required promotional material (Clause 14.1), meetings involving travel outside the UK (Clause 14.2) and material expressly covered by Clause 14.3 to be certified and recertified at intervals of no more than two years if still in use (Clause 14.5).

The Panel noted UCB's submission that not all pages on its corporate website required certification and recertification in line with the Code but all information on its corporate website was examined to ensure that it complied with the Code and was certified and recertified in line with Clause 14 where required.

The Panel noted UCB's explanation regarding the dates and codes which appeared at the bottom of its corporate website pages. In the bottom left-hand corner of every page was the same code and date (10MIS0004a/March 2011) which was an internal reference number and date assigned when the website was first commissioned. This number and date would therefore not change and did not indicate certification for purposes of the Code. In the bottom right-hand corner of each webpage was a statement 'Last update:.....' and the date recorded here might be different for each webpage indicating the date the particular webpage was last updated by UCB.

The Panel further noted UCB's submission that press releases on its website carried their own individual reference number and date of preparation which related to certification/examination of the material in line with the Code.

The Panel noted that although the website commissioning date of March 2011 appeared in the bottom left-hand corner of every webpage, the significance of the date was not explained. However, in the right-hand corner of every page, and in the same size font, the date of the last update was clearly stated. The complainant had not referred to any particular page of the website but on the assumption that he/she had at least looked at the page detailing support for patient organisations, the Panel noted that that page was last update on 26 March 2013. The Panel did not consider that the complainant had demonstrated that relevant pages of the website had not been recertified as required by the Code. No breach of Clauses 14.5 and 14.1 was ruled.

Complaint received	21 May 2013
Case completed	9 July 2013

GENERAL PRACTITIONER v TAKEDA

Promotion of Prostag

A general practitioner complained about the promotion of Prostag (leuprorelin acetate) at a meeting sponsored by Takeda UK. The complainant alleged that in response to a question about the licensed indication for Prostag being intramuscular in some cases and subcutaneous in others, the speaker stated that it did not matter which route was used. The complainant queried whether that represented promotion outwith the product licence.

The detailed response from Takeda is given below.

The Panel noted that as stated in the introduction to the Constitution and Procedure, a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had to make a decision based on the evidence before it. The Panel noted that the parties' accounts of the question and answer at issue differed; it was difficult to establish where the truth lay. The speaker and chairman had provided consistent accounts of the speaker's answer. The speaker's slides made no reference to any particular route of injection. The Panel considered that the complainant had not established that, on the balance of probabilities, the speaker had promoted Prostag outwith its marketing authorization as alleged. No breaches of the Code were ruled including no breach of Clause 2.

A general practitioner complained about the promotion of Prostag (leuprorelin acetate) at a meeting sponsored by Takeda UK Ltd. Prostag was a luteinising hormone-releasing hormone (LHRH) agonist indicated, *inter alia*, in the treatment of prostate cancer.

COMPLAINT

The complainant noted that at a Takeda-sponsored meeting entitled 'An Update on Prostate Cancer', held in May 2013, a delegate asked the speaker about the licensed indication for Prostag being intramuscular in some cases and subcutaneous in others. The speaker responded that it did not matter which route was used and the Takeda representative made no comment. The complainant queried whether this represented promotion outwith the product licence.

When writing to Takeda, the Authority asked it to respond in relation to Clauses 3.2, 9.1 and 2 of the Code.

RESPONSE

Takeda submitted that it had organised and funded the meeting in question for an audience of GPs and NHS Commissioners. The meeting was organised and attended by two Takeda representatives, chaired by an external consultant and the presentation in question entitled 'A Practice Based Case Study in the Management of LHRH agonist Provision'

was given by a health professional acting as a consultant to Takeda. Takeda stated that, given the complainant's concerns, it had asked the speaker, the chairman and the representatives present for their recollection of the question asked and the speaker's subsequent response. All parties agreed that the question was fully replied to in accordance with the product licence. Under the circumstances, the representatives did not consider that any further information was necessary. Both the speaker and the chairman agreed that there was no reason for the representatives to provide any further explanation.

Takeda submitted that the speaker had stated:

'The sequence of events was that I was asked about the variance of injection approaches for Prostag. I explained that the studies done on female patients for endometriosis involved a 90 degree angle approach intra muscularly and that the men's study was done with a 45 degree subcutaneous approach and as that is what was done during the trials, that is why there is a difference. I did say that clinically I do not know if it would make a difference, but that "those are the rules".

As I had said "those are the rules", and had already explained what they were and the reasons for the prescribing advice, there was no requirement for the Takeda representative to make any further comment.'

The chairman stated:

'...the question asked was:

Why is there a difference between how Prostag 3 DCS is administered for men and women?

[The speaker's] reply confirmed that following the studies, they concluded that the chosen licensed indication was subcutaneously for males and intramuscular for females.

[The speaker] further stated that he couldn't comment on whether there was a clinical difference, but emphasized that licensed indications stated should be the route of administration.

In response to your final query, I can see no reason why the representative from Takeda would need to make any further comments in respect to the licensed indication.'

Takeda submitted that both the speaker and chairman confirmed that the speaker's response was in line with the UK licence for Prostag 3 DCS, which was the product formulation referred to. Section 4.2 of the Prostag summary of product characteristics

(SPC) stated that for prostate cancer, the usual recommended dose was 11.25mg presented as a three month depot injection and administered as a single subcutaneous injection at intervals of three months and for endometriosis, the recommended dose was 11.25mg administered as a single intramuscular injection every 3 months for a period of 6 months only.

Takeda submitted that based on the above, the question was replied to within the letter and spirit of the Code; there was no promotion of or intention to promote, the use of Prostag 3 DCS outside its licence. Takeda thus denied a breach of Clause 3.2. Accordingly, Takeda was confident that high standards were maintained at all times and it thus denied breaches of either Clause 9.1 or Clause 2.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request from the Panel for comments on Takeda's submission, the complainant stated that in his view, the crucial section of Takeda's response was the statement '[The speaker] ...emphasised the licensed indications stated should be the route of administration'. The complainant submitted that his impression of what the speaker had said was the exact opposite and he was thus surprised that the representatives did not intervene.

The complainant stated that he had complained mainly to raise Takeda's awareness of the risks it ran due to its lack of vigilance; he hoped it would be

more cognisant of this in the future. The complainant expected that it would not be possible to take the matter further since the only evidence was hearsay.

PANEL RULING

The Panel noted that the parties' accounts of the question and answer at issue differed. It was one party's word against the other. The Panel noted the difficulty in dealing with such complaints; it was difficult to establish where the truth lay and to know exactly what was said by the speaker in response to the delegate's question.

As stated in the introduction to the Constitution and Procedure, a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had to make a decision based on the evidence before it. The speaker and chairman provided consistent accounts of the speaker's answer. The slides used by the speaker did not refer to any particular injection route. The Panel thus considered that the complainant had not established that, on the balance of probabilities, the speaker had promoted Prostag outwith its marketing authorization as alleged. No breach of Clause 3.2 was ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2.

Complaint received **23 May 2013**

Case completed **23 July 2013**

PFIZER v GLAXOSMITHKLINE

Votrient leavepiece

Pfizer complained about a **Votrient (pazopanib) GlaxoSmithKline leavepiece** entitled 'New data – **COMPARZ study**' (**COMPARing the efficacy, sAfety and toleRability of paZopanib vs sunitinib in first-line advanced and/or metastatic renal cell carcinoma**). The leavepiece also referred to the **PISCES study (Patient preference between pazopanib and sunitinib: results of a randomized, double-blind, placebo-controlled crossover study in patients with metastatic renal cell carcinoma)**.

Votrient was indicated, *inter alia*, in adults for the first-line treatment of advanced renal cell carcinoma and for patients who had received prior cytokine therapy for advanced disease. Pfizer marketed sunitinib (Sutent).

The detailed response from GlaxoSmithKline is given below.

Pfizer noted that the **COMPARZ study** was a **head-to-head, non-inferiority study**, to investigate the relative efficacy of **sunitinib and pazopanib** for the treatment of **metastatic renal cell cancer**. The protocol-defined criterion for non-inferiority was that the hazard ratio for progression-free survival would be contained within the upper bound of a two-sided 95% CI of 1.25 (subsequently tightened to 1.22 by the European Medicines Agency (EMA)). Submission of the **COMPARZ results** to the EMA was a post authorization measure for the conditional marketing authorization.

Pfizer noted that the leavepiece presented several analyses of data and it was claimed that **pazopanib** was non-inferior to **sunitinib** in terms of progression-free survival. It was not clear that the **intention-to-treat (ITT) population** was used to provide the progression-free survival comparison.

Pfizer noted that whilst the **ITT population** met the pre-defined criteria for non-inferiority, the **per protocol (PP) analysis** did not. The **ITT analysis** was an unusual and importantly non-conservative choice for a non-inferiority study. Pfizer referred to international and expert group guidance from the **US Food and Drug Administration (FDA)** and the **EMA** and submitted that the **PP analysis** was critical for clinicians to judge the totality of the data and make informed treatment decisions regarding these two medicines. Pfizer alleged that to present only the **ITT analysis** in the leavepiece but not label it as such was misleading; both the **ITT analysis** and the **PP analysis** should be presented in all promotional materials.

Importantly, the **Committee for Medicinal Products for Human Use (CHMP)** had recently recommended that, on the basis of all of the data, including the **COMPARZ study**, that **pazopanib** be granted a normal licence. This made it even more critical that

the **COMPARZ data** was presented transparently and ethically so that clinicians could make an informed treatment decision based on a good understanding of the relative efficacy of each medicine.

The Panel noted that the primary endpoint of the **COMPARZ study** was progression-free survival assessed by independent review, to be performed on the **ITT population**. In that regard the Panel noted the submissions about the relative merits of **ITT vs PP analyses** in non-inferiority studies and that both were associated with differing strengths and weaknesses. Statistical guidance did not prohibit the use of an **ITT analysis** in non-inferiority studies. The **EMA** appeared to consider that the **ITT analysis** and the **PP analysis** were equally important and that their use should lead to similar conclusions for a robust interpretation of the result.

The Panel noted that the **COMPARZ study** had been designed such that the primary analysis would be conducted on the **ITT population**; progression-free survival would be assessed by independent reviewers. The **CHMP**, amongst others, had accepted that this design was appropriate. The Panel noted **GlaxoSmithKline's** submission that the proposed study analysis plan had been reviewed by the **CHMP** and that although it had requested a tighter non-inferiority margin of 1.22 vs 1.25, it had not raised any concerns about the use of **ITT** as the primary analysis population. The Panel noted that in a sensitivity analysis on the **PP population**, the hazard ratios were very similar to those from the **ITT analysis** with confidence intervals that overlapped (**PP analysis 0.910 – 1.255 vs ITT analysis 0.8982 – 1.2195**). The Panel thus considered that the results of the **PP analysis** and the **ITT analysis** appeared to be consistent. The primary **ITT analysis** met the **CHMP** defined primary endpoint of an upper bound of no more than 1.22 and thus demonstrated non-inferiority between **Votrient** and **sunitinib**. The Panel noted that when progression-free survival was assessed by investigators the confidence interval was 0.863 – 1.154 which also satisfied the **CHMP** limits.

The Panel noted that the **COMPARZ study objectives** were set out on page 3 of the leavepiece and the primary endpoint was stated to be to evaluate non-inferiority in progression-free survival between **Votrient** and **sunitinib**. It was not stated that that analysis would be in the **ITT population**. A diagram depicted the patient numbers in each treatment arm ie **Votrient n=557** and **sunitinib n=553**. Patients randomized into a trial formed, by definition, the **ITT population**. Although the graphs on page 4 headed 'Primary Endpoint – PFS (independent review)' and 'Progression Free Survival (investigator review)' respectively did not state that the analysis was performed on the **ITT population**, a table embedded into the two graphs noted the patients numbers in

each treatment arm (ie Votrient n=557 and sunitinib n=553). In that regard the Panel considered that, although not specifically stated on page 4, readers could deduce, given the information on page 3, that the primary endpoint analysis was carried out on the ITT population. The Panel noted its comments above about the satisfaction of the CHMP primary endpoint. The Panel considered that although it would have been helpful to explicitly refer to the ITT population on page 4, on balance the failure to do so was not misleading. No breach of the Code was ruled.

The Panel considered that as the primary ITT analysis and the PP analysis were so similar, it was not misleading to refer only to the ITT analysis. No breach of the Code was ruled.

The Panel considered that the claims regarding the non-inferiority of Votrient vs sunitinib could be substantiated. No breach of the Code was ruled.

Upon appeal by Pfizer the Appeal Board noted that the primary endpoint of the COMPARZ study was met in that Votrient was shown to be non-inferior to sunitinib with respect to progression-free survival assessed by independent reviews performed on the ITT population.

The Appeal Board considered that as the graphs on page 4 included the same patient numbers as stated on page 3, it could be concluded that this was the ITT population and analysis. The Appeal Board noted that an ITT analysis more closely reflected clinical practice.

The Appeal Board noted the conflicting academic debate on the merits of ITT vs PP analysis. The Appeal Board noted that a sensitivity analysis of the PP population had been included in the COMPARZ study and that hazard ratios from that analysis were very similar to those from the ITT analysis with overlapping confidence intervals. The Appeal Board considered that the differences between the ITT and PP results were unlikely to translate as a meaningful difference to an individual patient. It appeared that the ITT and PP results were not inconsistent.

The Appeal Board noted that the CHMP had accepted that the design of the COMPARZ study was appropriate (subject to a tighter non-inferiority margin of 1.22) in that the primary endpoint was based upon the ITT analysis. The Appeal Board also noted that the COMPARZ study had been published in the New England Journal of Medicine.

Whilst it might have been helpful to label the ITT analysis, the Appeal Board noted its comments above and considered that Pfizer had not established that the failure to do so was misleading. The Appeal Board upheld the Panel's ruling of no breaches of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its comments above and considered that it was not misleading to refer only to the ITT analysis. The Appeal Board upheld the Panel's ruling of no breaches of the Code. The appeal on this point was unsuccessful.

The Appeal Board considered that claims regarding the non-inferiority of Votrient vs sunitinib could be substantiated and upheld the Panel's ruling of no breach of the Code. The appeal on this point was unsuccessful.

With regards to the claim on page 10 that 'COMPARZ complements the PISCES study which demonstrated patient preference for Votrient', Pfizer stated that the PISCES study was a two stage, randomized, cross-over study where patients received one cycle of each medicine (sunitinib and pazopanib) in turn, separated by a washout period. At the end of the study period, patients were asked which they would prefer to take assuming that both medicines were equally efficacious.

Pfizer stated that as non-inferiority trials could not prove equal efficacy, no claims about patient preference could be made for pazopanib because such claims would be based on a false assumption and would be misleading.

The Panel noted that the PISCES study looked at whether patients preferred Votrient, sunitinib or had no preference for either. In the Panel's view, patients had to enter such a study on the premise that the two medicines in question had equal efficacy. The Panel noted that in small print at the bottom of page 10, it was stated that patients were asked 'Now that you have completed both treatments, which of the two drugs would you prefer to continue to take as the treatment for your cancer, assuming that both will work equally well in treating your cancer?' The Panel did not consider that readers would view this explanation as a claim that Votrient and sunitinib had equivalent efficacy. Given the outcome of COMPARZ, a patient preference study based on the question above was not unreasonable; patients would not understand the question if they were asked to assume that the two medicines were non-inferior. In the Panel's view the claim at issue was not misleading as alleged and could be substantiated. No breach of the Code was ruled.

Upon appeal by Pfizer the Appeal Board considered that in order to determine preference it was acceptable that participants were first asked 'Now that you have completed both treatments, which of the two drugs would you prefer to continue to take as the treatment for your cancer, assuming that both drugs will work equally well in treating your cancer?'. The Appeal Board noted that COMPARZ had shown that pazopanib was non-inferior to sunitinib. Patients would understand the phrase 'work equally well' far more easily than the phrase 'non-inferior'. The Appeal Board noted that at the appeal hearing Pfizer agreed that the PISCES study design was appropriate.

The Appeal Board did not consider that the fact that the patient question appeared in small print at the bottom of the page and was linked to the claim 'COMPARZ complements the PISCES study which demonstrated patient preference for Votrient' implied that Votrient and sunitinib had equal efficacy. The patient question helped place the study in context. The claim was not misleading and

could be substantiated. The Appeal Board upheld the Panel's ruling of no breaches of the Code. The appeal on this point was unsuccessful.

Pfizer stated that the way that the data had been presented in the detail aid did not provide all of the evidence that clinicians required to make a decision about the relative merits of pazopanib and sunitinib. Pfizer noted that in the detail aid and at a major congress, GlaxoSmithKline had presented only the analysis where the endpoint of non-inferiority was met and had only published the PP analysis on its website. Pfizer alleged that this was a deliberate attempt to mislead, in breach of Clause 2.

The Panel noted its rulings above of no breach of the Code and consequently ruled no breach of Clause 2 of the Code which was upheld on appeal by Pfizer. The appeal on this point was unsuccessful.

Pfizer Limited complained about a Votrient (pazopanib) leavepiece (ref (UK/PAZ/0332/12) issued by GlaxoSmithKline UK Ltd, entitled 'New data – COMPARZ study' (COMPARing the efficacy, sAfety and toleRability of paZopanib vs sunitinib in first-line advanced and/or metastatic renal cell carcinoma). The leavepiece also referred to the PISCES study (Patient preference between pazopanib and sunitinib: results of a randomized, double-blind, placebo-controlled crossover study in patients with metastatic renal cell carcinoma).

Votrient was indicated, *inter alia*, in adults for the first-line treatment of advanced renal cell carcinoma and for patients who had received prior cytokine therapy for advanced disease.

Pfizer marketed sunitinib (Sutent).

GlaxoSmithKline explained that there were six medicines licensed to treat advanced renal cell cancer in treatment-naïve patients. The two medicines which had positive National Institute for Health and Care Excellence (NICE) guidance for first-line use were pazopanib and sunitinib both of which were tyrosine kinase inhibitors and licensed to treat advanced and metastatic renal cell carcinoma. Clinicians and patients increasingly looked to understand how these medicines compared with one another in terms of efficacy, safety and tolerability. Unfortunately this desire had been frustrated by a lack of head-to-head data.

GlaxoSmithKline undertook the COMPARZ and PISCES studies to provide clinicians and patients with robust data which directly compared pazopanib and sunitinib. The COMPARZ study focussed primarily on efficacy and assessed whether pazopanib was non-inferior to sunitinib in terms of progression-free survival (PFS). The PISCES study was an innovative study in the field of advanced renal cell cancer, designed to assess patient preference between the two medicines ie based on their experience of taking both, patients were asked if they preferred one or the other or neither. Since neither medicine was curative, patient preference was a particularly important consideration in advanced cancer.

GlaxoSmithKline stated that in its view these studies complemented one another. They addressed two different but important considerations which clinicians and patients would want to take into account when choosing between pazopanib and sunitinib for treating advanced renal cell cancer.

1 COMPARZ endpoint data

COMPLAINT

Pfizer noted that the COMPARZ study was a head-to-head, non-inferiority study, to investigate the relative efficacy of sunitinib and pazopanib for the treatment of metastatic renal cell cancer. The protocol-defined criterion for non-inferiority was that the hazard ratio for progression-free survival would be contained within the upper bound of a two-sided 95% CI of 1.25. The European Medicines Agency (EMA) subsequently required a tighter definition; the upper bound of a two-sided 95% CI of 1.22. Submission of results from the COMPARZ study to the EMA was a post authorization measure for the conditional marketing authorization as outlined in Annex II C 'Specific obligations to complete post-authorization measures for the conditional marketing authorization'.

Pfizer noted that on page 4 of the leavepiece, several analyses of data were presented and it was claimed on page 10 and elsewhere that pazopanib was non-inferior to sunitinib in terms of progression-free survival. Pfizer was concerned about the data presented in the leavepiece to evidence this claim. It was not clear from page 4 what analysis set was used to provide the progression-free survival comparison, nor was it clear from the study schema on page 3. It was apparent from a clinical study report published on GlaxoSmithKline's website and from inter-company dialogue that the intention-to-treat (ITT) population was presented here. The clinical study report provided the following results for the trial:

PFS (IRC-assessed, ITT population)		
	pazopanib (N=557)	sunitinib (N=553)
Median PFS, months (95% CI)	8.4 (8.3–10.9)	9.5 (8.3–11.1)
HR (95% CI)	1.0466 (0.8982–1.2195)	
PFS (IRC-assessed, PP [per protocol] population)		
	pazopanib (N=501)	sunitinib (N=494)
Median PFS, months (95% CI)	8.4 (8.3–10.9)	10.2 (8.3–11.1)
HR (95% CI)	1.069 (0.910–1.255)	

Whilst the ITT population met the pre-defined criteria for non-inferiority, the per protocol (PP) analysis did not. Pfizer submitted that the ITT analysis would be an unusual and importantly non-conservative choice for a non-inferiority study. Major international guidance stated the following:

US Food and Drug Administration (FDA), Draft FDA Guidance for industry, Non-Inferiority Clinical Trials 2010:

‘Good Study Quality A variety of study quality deficiencies can introduce what is known as a “bias toward the null,” where the observed treatment difference in an NI study is decreased from the true difference between treatments. These deficiencies include imprecise or poorly implemented entry criteria, poor compliance, and use of concomitant treatments whose effects may overlap with the drugs under study, inadequate measurement techniques, or errors in delivering assigned treatments. Many such defects have small (or no) effects on the variability of outcomes (variance) but reduce the observed difference C-T, potentially leading to a false conclusion of non-inferiority. It should also be appreciated that intent-to-treat approaches, which preserve the principle that all patients are analyzed according to the treatment to which they have been randomized even if they do not receive it, although conservative in superiority trials, are not conservative in an NI study, and can contribute to this bias toward the null.’

EMA, ICHE9:

‘5.2.3 Roles of the Different Analysis Sets

In general, it is advantageous to demonstrate a lack of sensitivity of the principal trial results to alternative choices of the set of subjects analysed. In confirmatory trials it is usually appropriate to plan to conduct both an analysis of the full analysis set and a per protocol analysis, so that any differences between them can be the subject of explicit discussion and interpretation. In some cases, it may be desirable to plan further exploration of the sensitivity of conclusions to the choice of the set of subjects analysed. When the full analysis set and the per protocol set lead to essentially the same conclusions, confidence in the trial results is increased, bearing in mind, however, that the need to exclude a substantial proportion of subjects from the per protocol analysis throws some doubt on the overall validity of the trial.

The full analysis set and the per protocol set play different roles in superiority trials (which seek to show the investigational product to be superior), and in equivalence or non-inferiority trials (which seek to show the investigational product to be comparable, see section 3.3.2). In superiority trials the full analysis set is used in the primary analysis (apart from exceptional circumstances) because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis, since the non-compliers included in the full analysis set will generally diminish the estimated treatment effect. However, in an equivalence or non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully.’

EMA points to consider on switching between non-inferiority and superiority:

‘In a non-inferiority trial, the full analysis set and the PP analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation.’

CONSORT statement:

‘In non-inferiority and equivalence trials, non-ITT analyses might be desirable as a protection from ITT’s increase of type I error risk (falsely concluding non-inferiority). There is greater confidence in results when the conclusions are consistent.’

The CONSORT statement further advised that when data was presented or published:

‘It should be indicated whether the conclusion relating to non-inferiority or equivalence is based on ITT or per protocol analysis or both and whether those conclusions are stable with respect to different types of analyses (eg, ITT, per-protocol). Conclusions should preferably be stated in terms of the prespecified non-inferiority or equivalence margin using language consistent with the aim of the trial.’

It was clear, then, that the PP analysis was critical in allowing clinicians to judge the totality of the data and allow them to make informed treatment decisions regarding these two medicines. Pfizer considered that to present only the ITT analysis in the leavepiece but not label it as such was misleading; both the ITT analysis and the PP analysis should be presented in all promotional materials.

Importantly, the CHMP had recently recommended that, on the basis of the totality of data presented to it, including the COMPARZ study, that pazopanib be granted a normal licence. This made it even more critical that the data from COMPARZ were presented transparently and ethically to allow clinicians to make an informed treatment decision based on a good understanding of the relative efficacy of each medicine.

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

RESPONSE

GlaxoSmithKline stated that COMPARZ was a randomised, open-label, head-to-head, non-inferiority study designed to evaluate PFS with pazopanib vs sunitinib. The primary analysis pre-specified in the COMPARZ protocol was PFS as assessed by independent review, to be performed on the ITT population. The study was powered to detect non-inferiority in terms of PFS between pazopanib and sunitinib. The protocol-defined criterion for non-inferiority was that the upper bound of the 95% confidence interval for the point estimate of the hazard ratio must be less than 1.25. As noted by Pfizer, this study was conducted, in part, to meet EMA requirements. GlaxoSmithKline noted that the EMA reviewed the design of COMPARZ and required a stricter criterion for establishing non-inferiority; insisting that the upper bound of the 95% confidence interval for the point estimate of the hazard ratio did not exceed 1.22.

Results relating to the primary endpoint of the COMPARZ study were clearly and prominently presented on page 4 of the leavepiece. Since the upper bound of the 95% confidence interval fell below the pre-specified non-inferiority margin (both the 1.25 margin defined in the protocol, and the stricter 1.22 margin required by the EMA) the study unequivocally met its primary endpoint and demonstrated non-inferiority of pazopanib to sunitinib. GlaxoSmithKline stated that it could thus claim that the COMPARZ study demonstrated that pazopanib was non-inferior to sunitinib in terms of PFS. The CHMP, the committee of the EMA which had reviewed this data, reached the same conclusion and stated that 'Based on the VEG108844 (COMPARZ) study and the fulfilment of the pre-set non-inferiority margin of HR 1.22, pazopanib is considered non-inferior to sunitinib with regard to PFS and OS'.

As a result of the COMPARZ study the CHMP recommended that the conditional marketing authorization granted to pazopanib be converted to a full marketing authorization. Furthermore, a paper which detailed the design, results and conclusion of the COMPARZ study had been accepted for publication by a major international peer reviewed journal. This clearly indicated that the peer review panel considered that the study was methodologically valid.

GlaxoSmithKline noted that whilst Pfizer was concerned about how the claim (that pazopanib was non-inferior to sunitinib in terms of PFS) was evidenced in the leavepiece, it had agreed in a teleconference with GlaxoSmithKline (Wednesday, 8 March) that the study met its pre-defined primary endpoint of non-inferiority for pazopanib compared with sunitinib based on the ITT analysis.

GlaxoSmithKline submitted that Pfizer's statement that 'for a non-inferiority study, the ITT analysis would be an unusual and importantly non-conservative choice' was factually incorrect and not supported by regulatory guidance or current statistical thinking. The debate on the relative merits of an ITT vs PP analysis remained on-going amongst academic statisticians, exemplified by the fact that the FDA guidance cited by Pfizer was distributed in March 2010 for comment purposes only and remained in draft format. The EMA guidance did not conclude that both ITT and PP analyses must meet a pre-defined non-inferiority margin, rather that they should lead to similar conclusions. GlaxoSmithKline believed this was the case with respect to the COMPARZ study, and this opinion was clearly supported by both the CHMP and the panel of journal peer reviewers.

Undertaking PP analyses had its own set of pitfalls and should not be considered a more reliably conservative choice. In particular:

- '... the corresponding test [on the per protocol set] of the hypothesis and estimate of the treatment effect may or may not be conservative depending on the trial; bias, which may be severe, arises from the fact that adherence to the study protocol may be related to treatment and outcome.' (Regulatory guidance 1998)
- 'Unfortunately it is possible to envisage

circumstances under which the exclusion of patients in a per protocol analysis might bias the results towards a conclusion of no difference – for example, if patients not responding to one of the two treatments dropped out early.' (Jones *et al* 1996)

- There was no universally agreed definition of what would constitute a PP population in an oncology trial. The PP analysis set was defined differently for different studies. As the study sponsor defined the criteria for exclusion, this in itself could introduce the question of bias. By comparison, there was a very clear and widely accepted definition for the ITT population.
- Two meta-analyses have compared the results of PP and ITT analyses. Both showed results that contradict Pfizer's claim that PP analysis was, by default, more conservative (Ebbutt and Firth 1998 and Brittain and Lin 2005).

GlaxoSmithKline considered that it was appropriate to base the primary endpoint of the COMPARZ study on the ITT population. Moreover, regulatory agencies, the trial steering committee which included a range of relevant independent international experts, ethics committees and the data safety monitoring board all considered that the study design was appropriate. Importantly, since the study was conducted, in part, to meet specific regulatory obligations, the CHMP, a committee of the EMA, reviewed the proposed study analysis plan in detail and requested the tighter non-inferiority margin of 1.22 but did not raise any concerns about the use of ITT as the primary analysis population.

GlaxoSmithKline submitted that as with most clinical trials, various sensitivity analyses were planned including one which assessed efficacy based on the PP population. A PP analysis excluded major protocol deviators and therefore, compared with the corresponding ITT analysis, invariably left fewer subjects available for analysis which resulted in a reduction in power and consequently wider confidence intervals.

The results obtained from the PP sensitivity analysis of COMPARZ were in line with those from the primary (ITT) analysis (table below). In particular, hazard ratios obtained from the PP analysis were similar to those from the ITT analysis with substantially overlapping confidence intervals. Predictably, the PP analysis included fewer subjects than the ITT analysis which resulted in a wider confidence interval.

Summary of relevant results from the COMPARZ study

PFS (IRC-assessed, ITT population) – primary analysis		
	pazopanib (N=557)	sunitinib (N=553)
HR (95% CI)	1.0466 (0.8982 – 1.2195)	
PFS (IRC-assessed, PP population) – sensitivity analysis		
	pazopanib (N=501)	sunitinib (N=494)
HR (95% CI)	1.069 (0.910 – 1.255)	

GlaxoSmithKline considered that Pfizer's statement that 'while the ITT population met the pre-defined criteria for non-inferiority, the per protocol analysis did not' was highly misleading. The non-inferiority margin was pre-defined purely in relation to the primary analysis (ITT) population and was never intended to be applied to the PP analysis. The study was therefore powered based on the primary (ITT) analysis. Had it been intended that the pre-defined criteria for non-inferiority be applied to the PP analysis, a larger sample size would have been required at the outset to take into account subjects who deviated from the protocol and were therefore not included in the PP analysis.

GlaxoSmithKline noted Pfizer's allegation that it was misleading to only present the ITT analysis but not label it as such and that both the ITT and the PP analysis should be presented in all materials.

In terms of only presenting the primary ITT analysis in the leavepiece, GlaxoSmithKline considered that this approach was acceptable and in line with usual practice. Inevitably, a leavepiece could only provide a summary of the enormous volume of data and analysis about a particular medicine. GlaxoSmithKline took great care to ensure that marketing materials presented information about a medicine in a fair and balanced way. Where marketing material was focussed on a particular clinical trial, this was typically achieved by:

- clearly describing the objectives and outlining the design of the trial
- prominently displaying the results of the primary endpoint, making it clear whether or not this has been met
- including a selection of the secondary endpoints likely to be of greatest interest to prescribers
- summarising safety considerations including both commonly experienced and particularly serious adverse events associated with the medicine.

In this case, GlaxoSmithKline did not consider it necessary to include the PP sensitivity analysis and the primary endpoint ie ITT analysis. There was general agreement that COMPARZ met its primary endpoint. GlaxoSmithKline along with the CHMP and a journal peer review panel had concluded that by meeting its primary endpoint, COMPARZ had demonstrated that pazopanib was non-inferior to sunitinib in terms of PFS. As the hazard ratios obtained from the sensitivity analysis were in line with those from the primary ITT analysis, GlaxoSmithKline considered that including this analysis would add little to the reader's understanding of the comparative efficacy of pazopanib and sunitinib.

GlaxoSmithKline did not consider that Pfizer's reference to the recommendations contained in the CONSORT statement was relevant to the leavepiece in question. The CONSORT group recommendations pertained to transparent reporting of trials and were designed to aid authors in the preparation of articles intended for publication. Reports of clinical trials

published in academic journals typically contained much greater detail than was usual in leavepieces and the like. GlaxoSmithKline considered that marketing materials should be judged against the requirements of the Code rather than the CONSORT guidance.

GlaxoSmithKline noted that additional data on the COMPARZ study was available on its website and included the PP sensitivity analysis along with other detailed analyses. It was standard practice for the company website to contain more detailed analyses of clinical trial results than would normally appear in a leavepiece. Furthermore, GlaxoSmithKline confirmed that the paper which had been accepted for publication discussed both the primary ITT efficacy analysis and the corresponding PP sensitivity analysis.

GlaxoSmithKline acknowledged that it was not stated that the primary efficacy analysis shown in the leavepiece was based on the ITT population. However, since ITT was a very common way of analysing data from clinical trials and this analysis was clearly presented as being the pre-specified primary endpoint of the COMPARZ study, GlaxoSmithKline strongly refuted any suggestion that it had misled clinicians by not labelling this analysis 'primary analysis based on ITT population'.

GlaxoSmithKline also noted that it was not unusual for materials which summarised particular studies, including leavepieces, detail aids, slide decks etc, not to state in detail exactly how particular endpoints had been analysed. For example, the RECORD-3 trial, a non-inferiority study which aimed to identify the best order in which to sequence treatment with everolimus and sunitinib in metastatic renal cell cancer, was recently presented as an oral abstract at the 2013 American Society of Clinical Oncology annual meeting; the analysis population was not stated in either the written abstract or during the oral presentation. Furthermore, there were examples of documents approved by the FDA and EMA wherein data from a non-inferiority study was presented from an ITT analysis and not explicitly labelled as such.

In summary, GlaxoSmithKline considered that the COMPARZ study was appropriately designed to assess the non-inferiority of pazopanib compared with sunitinib and that an entirely acceptable primary endpoint, based on analysis of the ITT population, was selected and accepted by regulatory authorities. The results of the study showed unequivocally that this endpoint was met. This view had clearly been supported by regulatory agencies and a journal peer review panel. On the basis of the COMPARZ study results, the CHMP had stated 'pazopanib is considered non-inferior to sunitinib with regard to PFS and OS' and, as a consequence, that 'The marketing authorization should no longer be subject to specific obligations'.

GlaxoSmithKline considered that the leavepiece presented a fair and balanced summary of the trial design and results of the COMPARZ study, in accordance with the Code. In particular, GlaxoSmithKline did not consider that the leavepiece was misleading because the PP sensitivity analysis

had not been included. In line with usual practice, the leavepiece prominently featured the primary endpoint of the COMPARZ study, included a fair and balanced selection of secondary analyses that provided prescribers with further useful information and adequately covered safety matters related to the prescription of pazopanib. It was not considered necessary to include the sensitivity analysis of efficacy based on the PP population since the results of this analysis were consistent with those of the primary (ITT) analysis.

GlaxoSmithKline thus denied breaches of Clauses 7.2, 7.3, 7.4 and 7.8.

In response to a request from the Panel for further information, GlaxoSmithKline submitted that in order to appropriately contextualise its response, it was important to reiterate the substance of Pfizer's complaint. Pfizer's concern arose from the fact that firstly, it was not stated in the leavepiece that the primary analysis was performed on the ITT population and secondly the leavepiece did not include a sensitivity analysis based on the PP population. GlaxoSmithKline disagreed that this breached the Code for the reasons stated above and it considered that current academic and regulatory opinion supported its approach.

Pfizer had verbally agreed that the COMPARZ study had met the protocol-defined primary endpoint demonstrating non-inferiority on ITT analysis. This was supported by both an opinion issued by the CHMP on 21 March 2013 and a peer review panel who had reviewed the COMPARZ manuscript on behalf of a leading international medical journal.

GlaxoSmithKline noted that Pfizer's concerns related to the way in which the results of the study had been presented in the leavepiece; the company had not raised any concerns about the power of the study and it therefore queried the Panel's request for justification on that point.

GlaxoSmithKline submitted that in a time-to-event analysis, study power was a function of the number of events observed (disease progression in this case), rather than the number of patients recruited. To achieve 80% power in respect of the study's primary endpoint (upper bound of the 95% confidence interval for the hazard ratio for progression-free survival by independent review committee (IRC) assessment using ITT analysis <1.25), it was calculated that 631 IRC-adjudicated progression events were required. To meet a tighter non-inferiority margin of 1.22, 794 events would be required to maintain 80% power.

In oncology studies which used an endpoint of PFS, there was frequently discordance between the number of patients deemed to have 'progressed' by the investigator vs those adjudicated to have progressed by the IRC. This typically resulted in a higher number of investigator-assessed PFS events compared with IRC-adjudicated events within any given data cut.

In line with the statistical analysis plan for

COMPARZ, the dataset was analysed once 631 IRC-adjudicated events had arisen. The analysis results were the first obligation of the conditional approval for pazopanib. The analysis included 659 IRC-adjudicated events and 730 investigator-assessed events.

Although the EMA had asked GlaxoSmithKline to analyse the COMPARZ dataset once 794 investigator-assessed events had taken place, once the results based on the 659 IRC-assessed and 730 investigator-assessed events had been reviewed, the CHMP was satisfied that non-inferiority with respect to its criteria had been established, and it withdrew the requirement that GlaxoSmithKline undertake a further analysis once 794 investigator-assessed progression events had occurred.

GlaxoSmithKline emphasised that study power was related to the risk of failing to detect a true positive result (Type II error) and not to the risk of generating a false positive result (Type I error). Having fewer than 794 investigator-assessed progression events included in the analysis simply increased the risk of failing to demonstrate 'true' non-inferiority. The risk of detecting 'false' non-inferiority was unaffected. Despite having only 730 patients available for analysis, the CHMP was satisfied that the data was sufficiently strong to demonstrate non-inferiority.

In line with accepted practice, the study had been powered in respect of the primary endpoint not in respect of a sensitivity analysis such as that performed on the PP population.

Assuming 'robustness' referred to by the Panel meant the degree of certainty associated with a particular result, GlaxoSmithKline believed that it was best described by the 95% confidence interval associated with that result. As fewer patients were available for the PP analysis compared with the primary ITT-based analysis, the confidence intervals were consequently wider but were almost entirely overlapping as illustrated in the table above which summarized the relevant results from the COMPARZ study.

GlaxoSmithKline considered that it was inappropriate to compare the IRC-assessed PP population result to the 1.22 margin because firstly the EMA-defined 1.22 margin was always associated with investigator-assessed data, and secondly, the PP population result was a sensitivity analysis. GlaxoSmithKline submitted that the acceptance of the data by the CHMP attested to its robustness.

GlaxoSmithKline enclosed the agenda and training slides which related to the meeting in which the leavepiece had been briefed out to its sales representatives. It had been a face-to-face meeting during which the COMPARZ data had been presented by the medical team. GlaxoSmithKline included a further briefing document about the differences between the PP and ITT analysis.

GlaxoSmithKline could not submit a copy of the paper about the COMPARZ study which was due to be published because of the journal's embargo

policy. GlaxoSmithKline had been asked not to share the manuscript with anyone until publication but would provide the Authority with a copy once the embargo had been lifted.

GlaxoSmithKline reaffirmed that the leavepiece was an accurate, fair and balanced summary of the comprehensive data package submitted to, reviewed and accepted by the CHMP and therefore it did not consider that it had breached Clauses 7.2, 7.3, 7.4 or 7.8 or that a breach of Clause 2 was warranted for the reasons detailed above.

PANEL RULING

The Panel noted Pfizer's submission that the PP analysis was critical in allowing clinicians to judge the totality of the data and allow them to make informed treatment decisions regarding these two medicines. The Panel further noted that Pfizer considered that to present only the ITT analysis in the leavepiece but not label it as such was misleading and that both the ITT analysis and the PP analysis should be presented in all promotional materials.

Pfizer had further stated that it was critical that the data from COMPARZ were presented transparently and ethically to allow clinicians to make an informed treatment decision based on a good understanding of the relative efficacy of each medicine.

The Panel noted that the primary endpoint of the COMPARZ study was progression-free survival assessed by independent review, to be performed on the ITT population. In that regard the Panel noted the submissions from both parties about the relative merits of ITT vs PP analyses in non-inferiority studies. The Panel noted that using either analysis was associated with differing strengths and weaknesses. Statistical guidance did not prohibit the use of an ITT analysis in non-inferiority studies. The EMA appeared to consider that the ITT analysis and the PP analysis were of equal importance and that their use should lead to similar conclusions for a robust interpretation of the result.

The Panel noted that the COMPARZ study had been designed such that the primary analysis would be conducted on the ITT population; progression-free survival would be assessed by independent reviewers. The CHMP, amongst others, had accepted that this design was appropriate. The Panel noted GlaxoSmithKline's submission that the proposed study analysis plan had been reviewed by the CHMP and that although it had requested a tighter non-inferiority margin of 1.22 vs 1.25, it had not raised any concerns about the use of ITT as the primary analysis population. The Panel noted that a sensitivity analysis on the PP population had been included in the study and that the hazard ratios from that analysis were very similar to those from the ITT analysis with confidence intervals that overlapped (PP analysis 0.910 – 1.255 vs ITT analysis 0.8982 – 1.2195). In that regard the Panel considered that the results of the PP analysis and the ITT analysis appeared to be consistent. The primary ITT analysis met the CHMP defined primary endpoint of an upper

bound of no more than 1.22 and thus demonstrated non-inferiority between Votrient and sunitinib. The Panel noted that when progression-free survival was assessed by investigators the confidence interval was 0.863 – 1.154 which also satisfied the limits set by the CHMP.

The Panel noted that the COMPARZ study objectives were set out on page 3 of the leavepiece and the primary endpoint was stated ie to evaluate non-inferiority in progression-free survival between Votrient and sunitinib. It was not stated that that analysis would be in the ITT population. A diagram depicting the 1:1 randomisation of patients included the patient numbers in each treatment arm ie Votrient n=557 and sunitinib n=553. Patients randomized into a trial formed, by definition, the ITT population. Although the graphs on page 4 of the detail aid headed 'Primary Endpoint – PFS (independent review)' and 'Progression Free Survival (investigator review)' respectively did not state that the analysis was performed on the ITT population, a table embedded into the two graphs noted the patients numbers in each treatment arm (ie Votrient n=557 and sunitinib n=553). In that regard the Panel considered that, although not specifically stated on page 4, readers could deduce, given the information on page 3, that the primary endpoint analysis was carried out on the ITT population. The Panel noted its comments above about the satisfaction of the CHMP primary endpoint. The Panel considered that although it would have been helpful to explicitly refer to the ITT population on page 4 of the detail aid, on balance the failure to do so was not misleading in that regard. No breach of Clauses 7.2 and 7.8 was ruled. This ruling was appealed by Pfizer.

The Panel noted Pfizer's concern that to present the ITT analysis without the PP analysis was misleading. The Panel noted its comments above about the consistency of the primary ITT analysis and the PP analysis and considered that as the results were so similar, it was not, in the particular circumstances of this case, misleading to refer only to the ITT analysis. No breach of Clauses 7.2 and 7.3 was ruled. This ruling was appealed by Pfizer.

The Panel considered that the claims regarding the non-inferiority of Votrient vs sunitinib could be substantiated. No breach of Clause 7.4 was ruled. This ruling was appealed by Pfizer.

APPEAL BY PFIZER

Pfizer stated that the Panel appeared to have carefully considered the correctness or otherwise of the primary endpoint used in the COMPARZ study and therefore whether the COMPARZ study could be used to claim non-inferiority of Votrient vs sunitinib. Pfizer did not contend that this study had failed to meet the primary endpoint defined in the protocol. Rather, Pfizer argued that, because of the statistical principles related to non-inferiority studies, it was misleading to present only the ITT analysis (which was not conservative in the non-inferiority trial setting as it was in superiority studies) without specifying that this was the analysis used, and failing to show the equally important PP analysis. A full

presentation of the results was critical in this context to maintain the highest standards of transparency.

Use of a single analysis of the endpoint in the setting of non-inferiority in the leavepiece

Pfizer noted that the Panel agreed that the EMA guidance stated that the ITT and PP analyses were of equal importance and that their use should lead to similar conclusions for a robust interpretation of the result. Pfizer submitted that from the results given below, it could be seen that the ITT and the PP analyses showed a magnitude of difference which might appear similar, (a hazard ratio of 1.046 and 1.069 respectively), in favour of sunitinib. The confidence intervals, though, did not lead to similar conclusions: the ITT suggested that the trial had met pre-defined criteria for non-inferiority, while this was not the case in the PP analysis.

Pfizer noted that the Panel had asked GlaxoSmithKline a number of supplementary questions about the power of the study. This suggested that the Panel considered that issues relating to the power of the study were crucial in explaining any potential differences between the hazard ratios of these two analyses. Pfizer alleged that GlaxoSmithKline's answers were inaccurate, confusing and misleading.

In particular Pfizer questioned why, when asked why more patients were not recruited to meet the stricter endpoint requested by the EMA, GlaxoSmithKline described time to event analyses and study power being a function of the number of patients recruited. In fact, the EMA gave GlaxoSmithKline permission to analyse two separate protocols together in order to provide the power, and a protocol amendment was undertaken to achieve this (The CHMP assessment report (2010) for pazopanib). It was unclear why GlaxoSmithKline did not disclose this.

Pfizer further questioned why, when asked what power the study had to detect non-inferiority given the stricter EMA requirements, GlaxoSmithKline stated that 'study power was related to the risk of failing to detect a true positive result (Type II error) and was not related to the risk of generating a false positive result (Type I error)'. While this was true for superiority trials, it was much more complicated in the non-inferiority setting where a lack of power could bias towards conclusions of non-inferiority (ie a false positive result). As a result, GlaxoSmithKline appeared to dismiss incorrectly the risk of underpowering a non-inferiority study. This answer from GlaxoSmithKline, which failed to demonstrate a clear and transparent understanding of the principles underlying non-inferiority design, again highlighted the serious risk that failure to present these data in their totality could give rise to similar misunderstandings amongst treating clinicians.

The Panel went on to ask GlaxoSmithKline about the robustness of the PP analysis given the smaller patient numbers. GlaxoSmithKline responded that the confidence intervals were wider for the PP analysis and that they overlapped entirely the ITT. In fact, the confidence interval was not much wider in the PP analysis relative to the ITT analysis, but the

whole estimate (point estimate for the hazard ratio as well as the upper and lower limits of the confidence interval) was shifted right, further in favour of sunitinib, and they did not overlap at the lower end.

GlaxoSmithKline suggested that reducing the number of events would make it less likely for non-inferiority to be shown, while in fact the opposite might be true. Even with smaller numbers in the PP analysis, which could bias the study towards a finding of non-inferiority, the study did not meet the non-inferiority criteria in the PP analysis. In an open-label study, that was of concern and a further reason why the PP analysis was so critical to an interpretation of this study.

Pfizer did not agree that the CONSORT statement did not apply to presenting the results of trials in marketing materials, and that the basic principles of the CONSORT statement were not the basic principles underpinning the Code. Given the very difficult nature of the statistical principles underpinning non-inferiority studies, the poor understanding of these studies amongst clinicians and the fact that COMPARZ was the first non-inferiority study conducted in kidney cancer the CONSORT statement required that the PP analysis be reported. For the same reasons, Pfizer expected the PP analysis be used in marketing materials.

The regulatory framework and why the COMPARZ study was acceptable to the CHMP and EMA

Pfizer noted that GlaxoSmithKline relied heavily in its response on the opinion of a journal peer review panel and the CHMP and the granting of a full marketing authorization subsequent to the COMPARZ study being submitted to the CHMP to justify the presentation of only one analysis in its marketing materials. Notwithstanding that the study had satisfied the CHMP, this must be taken in the context of why the COMPARZ study was requested and the role of the regulator in this regard.

First-line treatment of metastatic renal cell carcinoma was a crowded market. The first medicine of the modern era approved in this setting, sorafenib (Nexavar), was granted a marketing authorization in a pivotal study with a median progression-free survival (PFS) of 5.5 months (167 days) in a head-to-head study vs placebo (Nexavar summary of product characteristics (SPC)). Sunitinib demonstrated a PFS of 11 months vs an active comparator very soon after (Sutent SPC). Several years later, GlaxoSmithKline submitted the pivotal phase III trial of pazopanib vs placebo (study VEG105192) to the CHMP, which demonstrated a PFS of 11 months in patients treated with pazopanib (Votrient SPC). Although both sunitinib and pazopanib gave PFS of 11 months in their pivotal trials, these numbers could not be directly compared because there might have been differences in the baseline characteristics of the patients in the trials. Since the comparator arms were also different (placebo in the pazopanib trial and an active comparator, Interferon, in the sunitinib trial), cross trial comparisons of efficacy were not possible.

Pfizer alleged that GlaxoSmithKline proceeded with the placebo-controlled study despite advice,

in December 2006, that such a study would not be recommended for seeking a marketing authorization (CHMP assessment report (2010) for pazopanib). This advice was repeated in February 2007, before GlaxoSmithKline sought further advice in October 2007 as to what active comparator study the authority would recommend. The CHMP recommended a blinded, head-to-head study vs sunitinib (VEG 108844, later to be called the COMPARZ study). GlaxoSmithKline undertook the study in an open-label fashion (thereby increasing risk of bias, which was particularly problematic in the setting of non-inferiority).

Pfizer alleged that in granting the initial conditional licence for pazopanib, the CHMP assessed the pivotal phase III head-to-head study, along with the rest of the data package, and concluded that the risk-benefit assessment was favourable, and that pazopanib was an effective medicine. Despite this, and given the new therapies available by the time of the CHMP assessment of pazopanib, the CHMP stated 'Therefore, the CHMP was of the opinion that even though in the specific case of pazopanib it had been shown that the product was effective, an active comparator with other [tyrosine-kinase] inhibitors was necessary in order to rule out that the use of pazopanib would mean a loss of opportunity for the patients' (CHMP assessment report (2010) for pazopanib).

Pfizer alleged that by this stage the COMPARZ study was ongoing. While the CHMP then discussed the COMPARZ study in detail with GlaxoSmithKline and suggested some changes to the study (eg reducing the non-inferiority margin) it might be inferred from the EPAR and other publically available regulatory documents that the CHMP did not hold the COMPARZ study to the same regulatory requirements as for a pivotal non-inferiority study. This would explain why the CHMP assessment of COMPARZ would be at odds with the guidance published from the EMA which was unequivocal when it stated 'in a non-inferiority trial, the full analysis set and the PP analysis have equal importance and their use should lead to similar conclusions' (EMA guideline 2000, Schumi and Wittes, 2011). This had not been demonstrated in COMPARZ where one analysis led to a conclusion of non-inferiority, the other did not.

Pfizer alleged that the regulator required the head-to-head COMPARZ study to answer the question of relative efficacy and then made its decision to grant a full licence on the basis of the totality of the data presented. This was in the context of already having assessed significant additional data from GlaxoSmithKline on the benefits and risks of pazopanib. But it was crucial to note that clinicians did not have access to the same quality of data when making actual treatment decisions. Indeed clinicians had rightly demanded for some time that the same amount of data be given to them to help their decision making as was given to the regulators. Clause 7.2 stated that '... claims ... must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion,

exaggeration or undue emphasis. **Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'** (emphasis added by Pfizer).

Pfizer alleged that GlaxoSmithKline emphasised acceptance of the trial for publication by a peer reviewed journal as vindication of the trial being positive and the analysis presented in the leavepiece being fair and balanced. However, a study of the size and importance of COMPARZ should always be accepted for publication regardless of the result of the study, and so publication in a peer reviewed journal alone did not imply acceptance of non-inferiority. Crucially, as stated by GlaxoSmithKline, the peer review panel did require both the ITT and the PP analyses be submitted to the journal.

Pfizer finally noted that pazopanib was granted full approval in the US on the basis of the pivotal phase III trial vs placebo. The US regulator had not required COMPARZ to be submitted and had not judged the study against its own guidance.

The approach of other prescription medicines advertising authorities around the world in this setting

Pfizer alleged that non-inferiority in oncology was a relatively new approach, but was likely to increase, along with resultant advertising to clinicians, of a number of 'me too' small molecules such as pazopanib came to market. Although there was no specific guidance in the UK or European Code, the Canadian Pharmaceutical Advertising Advisory Board (PAAB) had issued a comprehensive document in this setting, which reiterated a number of the key points highlighted above and made a number of key recommendations:

Sample size: Under section 2 of the PAAB guidance, 'Key Pitfalls', it stated that 'unlike superiority trials, an underpowered non-inferiority trial may be more likely to produce an untrue positive result' and that type II error had heightened importance in non-inferiority trials and must be managed. If sample size was inadequate, a non-inferiority trial could lead to false claims of non-inferiority when a medicine was, in fact, worse than a comparator. The PAAB suggested that description of interim analyses, power calculations etc should be provided in all advertising materials. Although the management of power in this trial did not form part of Pfizer's original complaint, it was clear that the Panel considered it was a key concern, and Pfizer therefore believed that further clarity from GlaxoSmithKline was required on this point.

Analysis sets: The PAAB stated: 'For each analysis, provide the number of participants contributing to estimates of effectiveness. If the number is smaller than the intent-to-treat number, specify how the denominator was derived. (ie state from a per protocol analysis and associated criteria).

Both ITT and per protocol results should be assessed (and both should support the conclusion of non-inferiority).'

The PAAB stated that these analyses above should be included in all advertising materials.

For the reasons outlined above, Pfizer alleged that the presentation of the COMPARZ study in the leavepiece was in breach of Clauses 7.2, 7.3, 7.4, and 7.8.

RESPONSE FROM GLAXOSMITHKLINE

GlaxoSmithKline submitted that Pfizer had made a number of serious allegations, incorrect paraphrases and disparaging remarks and it addressed these first.

Pfizer alleged that GlaxoSmithKline had misled the Panel by not disclosing the details of a protocol amendment undertaken to adequately power the COMPARZ study. This issue was raised by Pfizer during previous inter-company dialogue and addressed by GlaxoSmithKline:

‘The clinical trial protocol for VEG108844 describes the inclusion of subjects enrolled in both VEG108844 and VEG113078 for evaluation in the pre-specified analyses of primary and secondary endpoints. As both VEG108844 and VEG113078 were of virtually identical design, pooling results of the two studies could be undertaken without statistical difficulties arising. The trial protocol, including the proposal to perform a pooled analysis has, in line with standard practice, been reviewed and accepted by the independent data safety monitoring board, regulatory authorities and various ethics committees.’ (GlaxoSmithKline’s letter to Pfizer dated 9 January 2013).

GlaxoSmithKline considered that as Pfizer had not pursued this dialogue further it had accepted the validity of pooling data obtained from both these protocols as constituting the pre-specified analysis of the COMPARZ study.

‘We are prepared not to pursue this section of our complaint further at this time. We understand that further data from trials VEG108844 and VEG113078 may be presented at ASCO GU. We hope that these further data go some way to answering our questions in this area. That said, we reserve the right to raise this issue again if, for example, the separate analyses are not presented or do not individually support the overall conclusions of the pooled analysis.’ (Pfizer letter to GlaxoSmithKline dated 15 January 2013).

GlaxoSmithKline submitted that Pfizer had not raised this issue during the course of this current complaint, either during inter-company dialogue or when it referred the complaint to the PMCPA. Since this matter did not appear relevant to any of the specific complaints which Pfizer referred to the PMCPA, GlaxoSmithKline did not believe that this issue needed to be addressed in its response to Pfizer’s complaint. GlaxoSmithKline therefore strongly refuted any suggestion that it had misled the PMCPA in its response to this complaint.

Pfizer stated that GlaxoSmithKline’s response to the PMCPA of 2 July was inaccurate and confusing. GlaxoSmithKline noted that Pfizer incorrectly paraphrased GlaxoSmithKline’s letter as follows:

- GlaxoSmithKline stated in its letter to the PMCPA (2 July 2013):

‘... study power is a function of the number of events observed (in this case disease progression), rather than the number of patients recruited.’

GlaxoSmithKline submitted that Pfizer incorrectly paraphrased this in its appeal as:

‘GlaxoSmithKline described time to event analyses and study power being a function of the number of patients recruited.’

- GlaxoSmithKline stated in its letter to the PMCPA (2 July 2013,):

‘... the confidence intervals are consequently somewhat wider, but were almost entirely overlapping’ [table 1 contained exact confidence interval values].’

GlaxoSmithKline submitted that Pfizer had incorrectly paraphrased this in its appeal as:

‘GlaxoSmithKline responded that the confidence intervals were wider for the PP analysis and that they overlapped entirely the ITT.’

GlaxoSmithKline submitted that the relevant confidence intervals from the COMPARZ study were as follows (COMPARZ results – www.GSK-clinicalstudyregister.com):

PFS (IRC-assessed, ITT population) – Primary analysis		
	pazopanib (N=557)	sunitinib (N=553)
HR (95% CI)	1.0466 (0.8982 – 1.2195)	
PFS (IRC-assessed, PP [per protocol] population) – Sensitivity analysis		
	pazopanib (N=501)	sunitinib (N=494)
HR (95% CI)	1.069 (0.910–1.255)	
PFS (Investigator-assessed, ITT population) – Sensitivity analysis		
	pazopanib (N=557)	sunitinib (N=553)
HR (95% CI)	0.998 (0.863 – 1.154)	

GlaxoSmithKline stated in its letter to the PMCPA (2 July 2013, page 2):

‘... having fewer than 794 investigator-assessed progression events included within the analysis simply increased the risk of failing to demonstrate “true” non-inferiority. The risk of detecting “false” non-inferiority is unaffected’.

GlaxoSmithKline submitted that Pfizer had incorrectly paraphrased this in its appeal as:

‘GlaxoSmithKline suggests that reducing the number of events would make it less likely for non-inferiority to be shown, while in fact the opposite may be true.’

GlaxoSmithKline was surprised that Pfizer had chosen to disparage both its and the CHMP's scientific work as follows:

- Pfizer commented in its appeal:

'... it might be inferred from the EPAR and other publically available regulatory documents that the CHMP did not hold the COMPARZ study to the same regulatory requirements as for a pivotal non-inferiority study. This would explain why the CHMP assessment of COMPARZ would be at odds with the guidance published from the EMA'

GlaxoSmithKline submitted that Pfizer was perfectly entitled to discuss its inferred conclusion of lower standards regarding the approach taken by the CHMP to the licensing of pazopanib with the regulatory authorities. However, GlaxoSmithKline was of the opinion that such concerns were not relevant to the complaint.

- Pfizer commented in its appeal in Point 2 below:

'GlaxoSmithKline go on to state that they had not tried to infer equivalence between the two medicines at all, as the non-inferiority design of the trial was clear throughout the detail aid. This is disingenuous.'

GlaxoSmithKline submitted that Pfizer's assertion of being disingenuous was disparaging and entirely unjustified. The non-inferiority design and result of the COMPARZ study was made abundantly clear throughout the leavepiece.

GlaxoSmithKline concurred with the Panel's conclusion with respect to this particular matter: 'The Panel did not consider that readers would view this explanation [of the question posed to patients in the PISCES study] as a claim that Votrient and sunitinib had equivalent efficacy.'

GlaxoSmithKline now addressed the points made by Pfizer in its appeal.

COMPARZ endpoint data

GlaxoSmithKline submitted that the COMPARZ study design, including choice of primary endpoint, primary analysis population and statistical power, was reviewed and accepted by the EMA as being adequate to meet GlaxoSmithKline's post-licence requirement to demonstrate non-inferiority for pazopanib vs sunitinib. Furthermore, the results of COMPARZ had been reviewed and accepted by the CHMP leading to its conclusion that the data demonstrated non-inferiority of pazopanib to sunitinib for progression-free survival. The same conclusion was reached by the peer review panel of a leading medical journal which demonstrated its acceptance of the trial methodology, result and importantly the conclusion of non-inferiority.

GlaxoSmithKline submitted that Pfizer's continued assertion that ITT analysis was 'not conservative in the non-inferiority trial setting as it was in superiority studies' in itself failed to demonstrate an

up-to-date evaluation of current statistical thinking. GlaxoSmithKline referred to its response above where the academic debate on the relative merits of ITT vs PP analysis in non-inferiority trials was discussed.

GlaxoSmithKline noted that the current Votrient SPC did not include the PP sensitivity analysis, nor did it state that the primary analysis of PFS was performed on the ITT population. Other examples of regulatory-approved documents presenting non-inferiority data in a similar fashion was provided in earlier correspondence.

GlaxoSmithKline also highlighted that the CHMP, journal peer review panel and Panel all concluded that the results of the PP analysis (a pre-specified sensitivity analysis) were consistent with the ITT analysis (primary analysis). This further supported GlaxoSmithKline's position that due to the consistency between the two results it was not, in this case, misleading to only refer to the ITT analysis in promotional materials, a conclusion also reached by the Panel.

GlaxoSmithKline considered that the leavepiece was not misleading and not in breach of Clauses 7.2, 7.3, 7.4 or 7.8.

GlaxoSmithKline subsequently provided the published version of the COMPARZ study (Motzer *et al* 2013). A copy was provided to Pfizer for comment.

FINAL COMMENTS FROM PFIZER

Pfizer was concerned that its intentions in its appeal had been misinterpreted. GlaxoSmithKline claimed that Pfizer had made some serious allegations, and used some incorrect paraphrasing and disparaging remarks. Pfizer responded to these in turn:

Serious allegations

Pfizer stated that it had discussed the pooling of protocols as part of inter-company dialogue between December 2012 and March 2013 and it accepted the explanation given by GlaxoSmithKline in relation to the protocol amendment. Pfizer questioned why GlaxoSmithKline failed to highlight key information in response to an inquiry from the Panel about the power of the COMPARZ study given the stricter EMA requirements. Pfizer simply noted that GlaxoSmithKline's response was factually inaccurate (by omission) and therefore confusing and misleading.

Incorrect paraphrases

Pfizer acknowledged that its appeal did not directly quote GlaxoSmithKline in some places. However, this did not materially impact the information it had conveyed, particularly as the Panel had the original letter from GlaxoSmithKline.

Disparaging remarks

Pfizer was surprised that GlaxoSmithKline considered that its appeal was disparaging, either to the CHMP or to GlaxoSmithKline. Pfizer clarified what it had stated:

- Pfizer did not disparage the work of the CHMP. Pfizer's appeal sought to explain why it might be possible that the CHMP would take the results of the COMPARZ study and grant a full licence to pazopanib, despite the two analysis sets (PP and ITT) clearly leading to differing conclusions (in ITT, non-inferiority was demonstrated, but in PP it was not). Pfizer did not reiterate its conclusions here.
- Pfizer did not intend to disparage GlaxoSmithKline in its appeal in Point 2 below when it stated that the company was being disingenuous when it claimed it was not trying to infer equivalence. However, given GlaxoSmithKline's response to this section indicating the misinterpretation of Pfizer's initial comments, it did concede that the word 'disingenuous' in that context was too strong.

APPEAL BOARD RULING

The Appeal Board noted that the primary endpoint of the COMPARZ study was met in that Votrient was shown to be non inferior to sunitinib with respect to progression-free survival assessed by independent reviews performed on the ITT population.

The Appeal Board noted that page 3 of the leavepiece included the COMPARZ study objectives and listed the primary and secondary endpoints. A figure depicted the study design showing a 1:1 randomisation of patients including the number of patients in each treatment arm (Votrient n=557 and sunitinib n=553) and although it was not stated patients randomised into a trial by definition formed the ITT population. The graphs on page 4 included the same patient numbers and although again it was not stated, it could be concluded from the previous page that this was also the ITT population and analysis. The Appeal Board noted that an ITT analysis more closely reflected clinical practice.

The Appeal Board noted that there was conflicting academic debate on the merits of ITT vs PP analysis. In relation to this particular case the Appeal Board noted that a sensitivity analysis of the PP population had been included in the COMPARZ study and that hazard ratios from that analysis were very similar to those from the ITT analysis with confidence intervals that overlapped (PP analysis 0.910 – 1.255 vs ITT analysis 0.8982 – 1.2195). The Appeal Board considered that the differences between the ITT and PP results were unlikely to translate as a meaningful difference to an individual patient. It appeared that the ITT and PP results were not inconsistent.

The Appeal Board noted that the CHMP had accepted that the design of the COMPARZ study was appropriate (subject to a tighter non-inferiority margin of 1.22) in that the primary endpoint was based upon the ITT analysis. The Appeal Board also noted that the COMPARZ study had now been accepted and published in the New England Journal of Medicine.

The Appeal Board accepted that it might have been helpful to label the ITT analysis. However the Appeal Board noted its comments above and considered that Pfizer had not established that the failure to explicitly state that the analysis was on

the ITT population, on Page 4 of the leavepiece, was misleading. The Appeal Board upheld the Panel's ruling of no breach of Clauses 7.2 and 7.8 of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its comments above about the CHMP, publication in a peer reviewed journal and that the ITT and PP analysis results were not inconsistent. The Appeal Board therefore considered that it was not misleading to refer only to the ITT analysis. The Appeal Board upheld the Panel's ruling of no breach of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful.

The Appeal Board considered that given its comments above the claims regarding the non-inferiority of Votrient vs sunitinib could be substantiated and it upheld the Panel's ruling of no breach of Clause 7.4. The appeal on this point was unsuccessful.

2 Claim 'COMPARZ complements the PISCES study which demonstrated patient preference for Votrient.'

This claim appeared on page 10 of the leavepiece.

COMPLAINT

Pfizer stated that the PISCES study was a two stage, randomized, cross-over study where patients received one cycle of each medicine (sunitinib and pazopanib) in turn, separated by a washout period. At the end of the study period, patients were asked which they would prefer to take assuming that both medicines were equally efficacious.

Pfizer stated that a non-inferiority trial could not prove equal efficacy. As such, no claims about patient preference could be made for pazopanib as such claims would be based on a false assumption and so also be misleading.

Pfizer alleged breaches of Clauses 7.2, 7.3 and 7.4.

RESPONSE

GlaxoSmithKline noted that PISCES was a randomised, double-blind, cross-over, patient preference study of pazopanib vs sunitinib in treatment-naïve locally advanced or metastatic renal cell carcinoma. The objective was to evaluate any difference in patient preference between the two medicines with all patients having taken both. Patient preference was an emerging, challenging area of research which was being undertaken increasingly across a range of therapeutic areas to help inform treatment decisions.

GlaxoSmithKline considered that patient preference in the setting of advanced renal cancer was a particularly important consideration for physicians and patients because:

- neither pazopanib nor sunitinib were generally considered to be curative, therefore the quality of the patient's remaining life was particularly important
- treatment with medicines such as pazopanib and sunitinib would often continue for a substantial proportion of the remaining, limited, lifespan of patients

- these medicines were associated with significant side effects which could substantially impact the quality of life of patients.

GlaxoSmithKline stated that in order to assess patient preference in isolation, it was necessary to ask patients to assume, for the purposes of the study, that both medicines worked equally well, particularly in the field of oncology where disease status did not always directly correlate with symptoms.

GlaxoSmithKline noted that in inter-company dialogue, Pfizer accepted that a patient preference study might have to assume equal efficacy between the medicines being compared, in order to elucidate patient preference in isolation. As stated in the leavepiece, patients were asked: 'Now that you have completed both treatments, which of the two drugs would you prefer to continue to take as the treatment for your cancer, assuming that both drugs will work equally well in treating your cancer?' (patients selected either first treatment, second treatment or no preference). Therefore the study was not based on a false assumption but instead, a necessary assumption for this type of research. The assumption of equal efficacy was considered to be reasonable when PISCES was designed since indirect comparative data suggested that pazopanib was similar to sunitinib in terms of efficacy in treatment-naive patients (HR 0.93, 95% CI 0.55, 1.56) (McCann *et al* 2010).

GlaxoSmithKline submitted that PISCES was initiated, conducted, analysed and presented before the outcome of the only head-to-head efficacy study (COMPARZ) was known. Therefore clinical equipoise existed around the relative efficacies of pazopanib and sunitinib when PISCES was undertaken. The design of PISCES, including the assumption used, was discussed with clinical experts, subjected to external scrutiny, and accepted by regulatory authorities and ethics committees. Moreover, it was unlikely that patients to whom the question was addressed would have understood the difference between one treatment being non-inferior to another or working equally well.

GlaxoSmithKline submitted that the non-inferiority design of the COMPARZ study was abundantly clear throughout the leavepiece, including the summary given on page 10. The final bullet point on page 10 which Pfizer was concerned about stated that 'COMPARZ complements the PISCES study which demonstrated patient preference for VOTRIENT (70% preferred VOTRIENT vs. 22% who preferred sunitinib (8% no preference; 90% CI (for difference); 37.0%-61.5%; $p < 0.001$).' which was a straightforward summary of the results from the PISCES study. The footnote at the bottom of page 10 clarified the study design.

GlaxoSmithKline stated that it had not tried to infer equivalence of pazopanib and sunitinib in terms of efficacy and did not believe that readers would be left with that impression. The non-inferiority design and result from the COMPARZ study were prominently described throughout the leavepiece.

GlaxoSmithKline submitted that it had included the final bullet point on page 10 because it considered that clinicians treating patients with renal cell cancer would want to consider a range of factors when deciding which treatment to prescribe. These factors included efficacy, adverse event profile and patient preference, alongside various patient-specific factors. Therefore GlaxoSmithKline considered that presenting data which focussed on patient preference alongside efficacy data was useful to clinicians. The PISCES trial design and assumption were transparent in the leavepiece. In particular, by presenting both PISCES and COMPARZ data together, clinicians could interpret the PISCES data, knowing that for the purposes of the study patients were asked to assume that both treatments work equally well, in light of the non-inferiority demonstrated by the head-to-head efficacy results from COMPARZ. Clinicians would be in the best position to make appropriate prescribing decisions by having a clear appreciation of the objectives, design, results and limitations of both studies. GlaxoSmithKline stated that it did not consider that because patients had been asked to make a necessary assumption, the results of such a study could never be used in a promotional context. As previously acknowledged by Pfizer, that patients were asked to assume that both medicines under investigation worked equally well was a necessary feature of the design of this kind of study. The design of PISCES, alongside the key study result, was transparently presented in leavepiece. GlaxoSmithKline reiterated that the PISCES study did not and was never intended to support a claim of equivalence. GlaxoSmithKline thus did not consider that page 10 of the leavepiece was misleading and it denied breaches of Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel noted that the PISCES study was established to determine whether patients preferred Votrient, sunitinib or had no preference for either. In the Panel's view patients had to enter such a study on the premise that the two medicines in question had equal efficacy. The Panel noted that, in small print, at the bottom of page 10 of the leavepiece it was stated that patients were asked 'Now that you have completed both treatments, which of the two drugs would you prefer to continue to take as the treatment for your cancer, assuming that both will work equally well in treating your cancer?' The Panel did not consider that readers would view this explanation as a claim that Votrient and sunitinib had equivalent efficacy. The Panel considered that given the outcome of COMPARZ, a patient preference study based on the question above was not unreasonable; patients would not understand the question if they were asked to assume that the two medicines were non-inferior. In the Panel's view the claim at issue was not misleading as alleged and could be substantiated. No breach of Clauses 7.2, 7.3 and 7.4 were ruled.

APPEAL BY PFIZER

Pfizer noted that the PISCES study required an assumption of equal efficacy. It was clear that equality of treatments could not be claimed from a non-inferiority study such as the COMPARZ study as a series of strict guidelines underpinned the conduct of equivalence studies, which had not been adhered to in COMPARZ (rightly, as COMPARZ was never intended as an equivalence study). Patient preference was indeed a challenging and emerging area, but it was crucial to guard against the use of such flawed studies to be used in a promotional context. In terminal cancer, while quality of life and symptomatology were important measures, they could never be removed from the primary requirement of tumour control as had been done in the PISCES trial. As such, it was misleading to state that a certain number of patients preferred one medicine over another without being told there might be differences in how well their cancer responded.

Pfizer noted that in its response, GlaxoSmithKline contended that the PISCES study was 'not based on a false assumption but instead, a necessary assumption ...'. Pfizer alleged that the assumption of equal efficacy was based on cross trial comparisons, which were not acceptable under the Code. GlaxoSmithKline had further suggested that since PISCES was conducted before COMPARZ, it did not know about the relative benefits and therefore 'clinical equipoise existed' between sunitinib and pazopanib. Pfizer stated that the natural conclusion of that statement was that, in the absence of evidence to the contrary, all medicines could be assumed to be equal: an assumption which could not be credible.

Pfizer noted that GlaxoSmithKline had stated that it had not tried to infer equivalence between the two medicines at all, as the non-inferiority design of the trial was clear throughout the leavepiece. Pfizer alleged that this was disingenuous. For the reasons outlined above, Pfizer alleged that the presentation of the PISCES study in the leavepiece was in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE FROM GLAXOSMITHKLINE

GlaxoSmithKline submitted that prescribing decisions were multifaceted and it was often unrealistic to expect a single clinical trial to provide all the information a clinician was likely to find useful in deciding which medicine to prescribe in a particular situation.

GlaxoSmithKline submitted that the PISCES study was the first of its kind in advanced renal cell cancer and designed to assess patient preference for pazopanib vs sunitinib. In order to assess patient preference in isolation it was necessary to ask trial subjects to assume that the medicines worked equally well. The assumption was not unreasonable based on the data available at the time, including a published adjusted indirect comparison (not simply a cross trial comparison as stated by Pfizer) cited by GlaxoSmithKline previously.

GlaxoSmithKline submitted that the question posed to patients 'Now that you have completed both treatments, which of the two drugs would you prefer to continue to take as the treatment for your cancer, assuming that both drugs will work equally well in treating your cancer?' (patients selected either first treatment, second treatment or no preference) was phrased in a way that they were likely to easily understand – a point agreed by the Panel which stated that, 'patients would not understand the question if they were asked to assume that the two medicines were non-inferior'.

GlaxoSmithKline submitted that the question posed to patients was shown in the leavepiece in order for clinicians to adequately understand the design of PISCES and thus appropriately interpret the results of the study. The question was not presented in a way which GlaxoSmithKline believed was likely to be interpreted by readers as implying that equivalence had been demonstrated between pazopanib and sunitinib. Had GlaxoSmithKline not included details of the question posed to patients, the leavepiece might be judged to be misleading due to lack of transparency.

GlaxoSmithKline submitted that as discussed above, it was valuable to clinicians to understand the results of both the COMPARZ and PISCES studies presented in this leavepiece:

GlaxoSmithKline considered that the leavepiece was not misleading and not in breach of Clauses 7.2, 7.3 or 7.4.

FINAL COMMENTS FROM PFIZER

Pfizer noted that the claim 'COMPARZ complements the PISCES study which demonstrated patient preference for VOTRIENT ...' was qualified by a footnote which revealed that patients were asked to assume both medicines worked equally well before being asked their preference. If the COMPARZ study did not confirm equal efficacy (which GlaxoSmithKline and Pfizer agreed it did not), then Pfizer was unclear in what way the studies were complementary.

APPEAL BOARD RULING

The Appeal Board noted that the PISCES study was designed to demonstrate patient preference between Votrient, sunitinib or no preference. The Appeal Board considered that in order to determine preference it was acceptable that participants were first asked 'Now that you have completed both treatments, which of the two drugs would you prefer to continue to take as the treatment for your cancer, assuming that both drugs will work equally well in treating your cancer?'. The Appeal Board noted that COMPARZ had shown that pazopanib was non-inferior to sunitinib. Patients would understand the phrase 'work equally well' far more easily than the phrase 'non-inferior'. The Appeal Board noted that Pfizer's representatives at the appeal agreed that the PISCES study design was appropriate.

The Appeal Board did not consider that the fact that the patient question appeared in small print at the bottom of page 10 linked to the final bullet point which included the claim 'COMPARZ complements the PISCES study which demonstrated patient preference for Votrient' implied that Votrient and sunitinib had equal efficacy. The patient question helped place the study in context. The Appeal Board considered therefore that the claim in question 'COMPARZ complements the PISCES study which demonstrated patient preference for Votrient...' was not misleading and could be substantiated. The Appeal Board upheld the Panel's ruling of no breaches of Clauses 7.2, 7.3 and 7.4. The appeal on this point was unsuccessful.

3 Alleged breach of Clause 2

COMPLAINT

Pfizer stated that the way that the data had been presented in the detail aid did not provide all of the evidence that clinicians required to make a decision about the relative merits of pazopanib and sunitinib. Pfizer was surprised that in the detail aid and at a major congress, GlaxoSmithKline had presented only the analysis where the endpoint of non-inferiority was met and had only published the PP analysis on its website. Pfizer alleged that this was a deliberate attempt to mislead, in breach of Clause 2.

RESPONSE

GlaxoSmithKline did not consider that the leavepiece breached Clause 2 for the reasons detailed in Points 1 and 2 above. The leavepiece was an accurate, fair and balanced summary of the comprehensive data package submitted to, reviewed and accepted by the CHMP.

PANEL RULING

The Panel noted its rulings above of no breach of the Code and consequently ruled no breach of Clause 2 of the Code.

APPEAL BY PFIZER

Pfizer alleged that for reasons set out above, that the lack of transparency in the presentation of trial results could be significantly detrimental to the decision making of treating clinicians. This was compounded by the historical context that when these data were originally presented, the EMA had not yet ruled that the trial had satisfied its requirements.

Pfizer alleged that as information given to the Panel by GlaxoSmithKline was incorrect in several places, including a significant lack of clarity in the responses relating to sample size, there had been a serious failure to maintain high standards and therefore a breach of Clause 2.

RESPONSE FROM GLAXOSMITHKLINE

For the reasons set out above, GlaxoSmithKline did not believe that a breach of Clause 2 was warranted. GlaxoSmithKline remained confident that the leavepiece complied with the Code.

FINAL COMMENTS FROM PFIZER

Pfizer provided no further comments on this point.

APPEAL BOARD RULING

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

Complaint received

28 May 2013

Case completed

11 September 2013

WARNER CHILCOTT v TILLOTTS

Disguised promotion of Octasa in educational supplement

Warner Chilcott UK complained about the promotion of Octasa (mesalazine modified-release tablets) by Tillotts Pharma UK. The material at issue was a journal supplement published in the British Journal of Clinical Pharmacy. Warner Chilcott marketed Asacol (mesalazine modified release).

The detailed response from Tillotts is given below.

Warner Chilcott submitted that the supplement looked like a non-promotional, educational update – as indicated by its title ‘Educational update’ – produced by two independent health professionals and formatted in the house style of The British Journal of Clinical Pharmacy. These features were not consistent with a promotional supplement. The Code was explicit on this point and clearly indicated that promotional material in journals should not resemble independent editorial matter.

The Panel noted that Tillotts had provided data and reviewed and approved the article. The supplement was entitled ‘Introducing Octasa MR (mesalazine) – The lowest cost, oral, pH-dependent, modified-release mesalazine formulation available?’. Octasa prescribing information was included. The Panel considered that Tillotts was inextricably linked to the production of the supplement. Further, the company had submitted that it had provided reprints of the supplement to support Octasa, vs Asacol and had cited it in other materials. In the Panel’s view, Tillotts was thus responsible under the Code for the content of the supplement.

The front cover of the supplement was headed ‘Educational update’ which was underlined in red. The names of two independent authors appeared in the middle of the front cover. The outside top corner of each page of the article which made up the supplement, featured a red box labeled ‘Educational update’ in bold white type. A declaration of sponsorship appeared at the bottom of the cover page and again at the end of the article on page 3; the Octasa prescribing information appeared on page 4.

The Panel noted Tillotts’ involvement with the material and considered that although there were elements to show that the supplement was a promotional piece, its prominent characterisation as an ‘Educational update’ was such that the promotional nature of the material was disguised. In this regard, the Panel further noted Warner Chilcott’s submission that the supplement was formatted in the house style of the journal. Although the Panel had not been provided with a copy of The British Journal of Clinical Pharmacy, it noted that a paper previously published in the same journal, had a similar three column layout and heading structure. A breach of the Code was ruled.

Warner Chilcott noted that the font size of the declaration of sponsorship statement was disproportionately small and the reader could easily miss it at the foot of the first page. Even if this declaration was read, claims for Octasa had already been made earlier on the page.

The Panel noted that Tillotts’ declaration of sponsorship appeared on the front cover of the supplement and again at the end of the article. The declaration on the front cover was at the bottom of the page in small white type (a lower case ‘m’ was less than 2mm high) on a dark grey background. The dark grey band at the bottom of the page occupied 22% of the cover depth; the declaration of sponsorship statement within that band occupied 5% of the cover depth. The declaration statement was below larger type, on the same dark grey background, which referred to the associated journal. All other text on the cover was similarly in bigger and/or bolder type. The prominence of the heading ‘Educational update’, the title of the article and the author’s names and affiliations was emphasized by the bold white type in which they were written appearing on a black background. The red underlining of ‘Educational update’ kept the reader’s eye to the top or middle of the page. In the Panel’s view, the declaration of sponsorship was such that the reader’s eye would not be drawn to what appeared to be ‘the small print’ at the bottom of the page. In that regard the Panel did not consider that the statement was sufficiently prominent to ensure that readers were aware of it at the outset. A breach of the Code was ruled.

The claim ‘Introducing Octasa MR (mesalazine) – The lowest cost, oral, pH-dependent, modified-release mesalazine formulation available?’ appeared as the title of the supplement and of the article. Warner Chilcott did not accept that the question mark at the end of the title altered the nature of this wording, ie it was a claim for Octasa MR. Although no direct attempt to substantiate this claim was made, the reader was introduced in the first paragraph of the article to a list of seven available modified-release mesalazine products. No cost data were presented yet the title implied that Octasa was the cheapest option.

However, even if taking a cost minimisation approach, which might be questionable with no head-to-head clinical data for any of these products vs Octasa, the acquisition cost of mesalazine therapy should also take into consideration the prescribed daily dosage of mesalazine which varied by product and indication. Using the recommended dosing schedules and the prices presented in MIMS, May 2013, it was clear that there were mesalazine products/doses available in the UK with a lower acquisition cost than some daily doses of Octasa, including pH-dependent, modified release tablets.

Furthermore, this claim implied that both Octasa preparations were equivalently priced, which was not so; the daily cost of 2.4g/day mesalazine was greater for Octasa MR 800mg tablets than for Octasa MR 400mg tablets. Clearly both Octasa products could not be the lowest cost formulation available as one was more expensive than the other. Thus, to make a broad claim that Octasa MR was the lowest cost, oral, pH-dependent, modified-release mesalazine formulation available was inaccurate, misleading and incapable of substantiation.

In the Panel's view, although the title was presented as a question, readers would assume it was a claim ie that Octasa MR was the lowest cost, oral, pH-dependent, modified-release mesalazine available.

The first paragraph of the article introduced the reader to the seven modified-release mesalazine preparations which were available until the end of 2012. In that regard the Panel considered that the claim would be seen in the context of these seven medicines ie that Octasa was the lowest cost compared with them all. The Panel noted that additional data provided by Tillotts showed that Octasa MR 400mg tablets (2.4g/day) was the least expensive treatment option for acute treatment. However, for maintenance therapy a dose of Salofalk 1.5g was the least expensive option and Pentasa sachets were also less expensive than Octasa given that the highest maintenance dose of Octasa was 2.4g/day.

The Panel considered that the basis of the claim at issue had not been made abundantly clear. It was not clear as to which doses were included and if the claim related to acute treatment, maintenance treatment or both. The Panel considered that the claim was misleading as alleged and it could not be substantiated; breaches of the Code were ruled.

Warner Chilcott noted the statement 'This article describes how the launch of Octasa MR (Tillotts Pharmaceuticals) provides an opportunity to keep costs down without compromising patient care' appeared as part of the sub-heading to page 1 of the article. Warner Chilcott stated that in its view, the article neither presented nor referred to any evidence or data relating to the clinical benefits of Octasa in patient care. The supplement discussed the in vitro dissolution characteristics and cost differences between Asacol MR 400mg/800mg tablets and Octasa (Mesren) MR 400mg/800mg tablets. It appeared therefore that the statement 'without compromising patient care' was based purely on the extrapolation of in vitro data to the clinical situation and implied that without clinical evidence, interchanging the products discussed would not affect patient management or compromise patient care. To make this assumption without clinical data to show that it was of direct relevance and significance was misleading, in breach of the Code.

The Panel noted that the statement at issue was the second sentence to the subheading on page 1 of the article. The sub-heading, in full, read:

'The discontinuation of Mesren MR (mesalazine' Teva Pharmaceuticals) could have considerable cost implications for the NHS. This article describes how the launch of Octasa MR (Tillotts Pharmaceuticals) provides an opportunity to keep costs down without compromising patient care.'

The Panel noted that with the discontinuation of Mesren, patients previously taking that medicine would have to be switched to an alternative mesalazine product. The Panel further noted that Octasa was, as stated in the article, essentially a rebrand of Mesren; the formulation of both medicines was the same. In the Panel's view, patients switching from Mesren to Octasa should not notice a clinical difference in therapy. The Panel considered that in the context of the discontinuation of Mesren MR, the statement at issue was not misleading as alleged. No breach of the Code was ruled.

Warner Chilcott submitted that whilst the supplement referred to the British Society of Gastroenterology (BSG), the European Crohn's and Colitis Organisation (ECCO) and the British National Formulary (BNF) guidelines and statements, it was quick to disregard the caution represented by these bodies in relation to indiscriminate switching between mesalazine brands and the recommendation to prescribe modified-release mesalazine by brand. To date, there had been no head-to-head clinical studies between Octasa and any other mesalazine and very few head-to-head clinical studies between the different modified-release mesalazines in general. Absence of evidence showing clinical differences between mesalazines (because these studies had not been conducted) was not equivalent to evidence demonstrating no clinically significant differences between the mesalazines, hence the caution in the guidelines that these products should not be considered interchangeable. Dismissal of these cautions and recommendations supported Tillotts' aim to have mesalazine patients indiscriminately switched to Octasa and misrepresented the guidelines in this way was misleading and did not encourage the rational use of Octasa.

Furthermore, Warner Chilcott noted the comment that the BNF statement was 'originally made before the introduction of Mesren MR 400mg and Octasa MR 400mg to the UK market'. Whilst that might or might not be true (Mesren MR 400mg tablets were first licensed in the UK in November 2003) the comment implied that the BNF's position was outdated and could be further disregarded on these grounds. Warner Chilcott noted that the BNF was updated regularly and as it continued to use this statement, it presumably reflected the BNF's current position and was not an outdated recommendation as implied. Warner Chilcott alleged that this section of the supplement misled by distortion and failed to encourage the rational use of Octasa.

The Panel noted that the first section of the journal supplement introduced the reader to seven modified release mesalazine preparations and then stated that the article would describe some

of the similarities and differences of three of them – Mesren, Octasa and Asacol. The next section of the article referred to prescribing guidelines and that the BSG and ECCO had recommended that modified-release mesalazine should be prescribed by brand. It was stated however, that both guidelines appeared to suggest that there was little in the way of significant differences between available products with regard to important clinical outcomes. It was noted that the BNF statement which advised that oral mesalazine preparations should not be considered interchangeable was made before Mesren and Octasa had been introduced to the UK market.

The Panel considered that overall, the take home message was that it was not important to prescribe any modified-release mesalazine by brand and that they were all essentially interchangeable. In that regard the Panel noted that the sub-heading referred to 'modified release mesalazine' and so it appeared that the subsequent discussion was not restricted in its scope to Asacol, Mesren and Octasa. The Panel considered that this was misleading. A breach of the Code was ruled. The Panel did not consider that the information encouraged the rational use of Octasa. A breach of the Code was ruled.

Warner Chilcott noted the paragraph entitled 'Are there any significant differences between Asacol MR and Octasa MR?' despite an acknowledgement in the supplement that there was no comparative clinical data for Octasa vs Asacol MR. Instead, the article focussed on data from in vitro dissolution studies to make a case for (clinical) similarity between Asacol and Octasa. However, the methodology of these in vitro studies made it impossible to draw any meaningful conclusions about the similarities or differences between these products in vivo, let alone in various stages of disease activity in patients with ulcerative colitis. Warner Chilcott submitted that in vitro dissolution studies could not fully reproduce the conditions of the gastrointestinal tract in patients with ulcerative colitis. Furthermore, no statistical comparisons between the findings for Mesren and Asacol were presented and no in vitro/in vivo correlation had been established to indicate the potential clinical significance of the findings. Warner Chilcott noted that Fadda and Basit (2005), presented in the supplement, commented on the poor in vitro/in vivo correlations obtained for pH-responsive, modified-release dosage forms. Thus, any conclusions about the significance of the findings of these in vitro data were impossible and attempting to do so in this manner was misleading.

The Panel noted that in the section of the supplement entitled 'Are there any significant differences between Asacol MR and Octasa MR?' it was clearly stated that 'Octasa MR has not been compared directly in a clinical study with Asacol MR'. The Panel considered, however, that most readers would read the rest of the section and assume, even in the acknowledged absence of clinical data, that because the in vitro dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to

show that this was so. The Panel considered that the supplement was misleading in this regard. A breach of the Code was ruled.

Warner Chilcott noted that the y-axis of a graph was unlabelled and so it was unclear and ambiguous as to what was presented; it was impossible for the reader to interpret the findings presented. Warner Chilcott alleged that Tillotts had thus failed to maintain high standards in terms of representing the data and reviewing the article before publication.

The Panel noted that the graph was referenced to 'Tillotts Pharma 2012. Data on file' and headed 'Dissolution of Mesren MR 400mg vs Asacol Mr 400mg and 800mg'. The y-axis was not labelled and so in that regard the Panel considered that the graph did not reflect the evidence clearly. The Panel ruled a breach of the Code. The Panel further considered that the use of a poorly labelled graph meant that high standards had not been maintained. A breach of the Code was ruled.

Warner Chilcott alleged that the figure presented for the annual cost of Asacol, 2.4g/day, should be £715.58 and not £715.40 as shown. This error meant that all data derived from this figure was also inaccurate.

Warner Chilcott further submitted that the table was misleading in that it failed to take into account possible changes of dose through a year as patients responded, or not, to therapy. Failure to take this into account in the costs therefore presented an artificial and misleading scenario that would not be encountered in clinical practice and therefore this table presented inflated and unrealistic cost savings that could never be achieved.

Warner Chilcott further submitted that the table failed to state that to obtain the proposed cost savings, the calculations assumed that all 300 patients (the typical number of patients with ulcerative colitis in an average primary care trust (PCT)) would be switched from Asacol to Octasa. This was simply not the case. Although Asacol was the market leader, it had only approximately 40% of market share. As this had not been taken into account, the figures proposed were inflated and misleading.

Other factors omitted from the calculations presented in the table were the cost of implementing such a switch and the management of any relapses or other adverse events. Warner Chilcott was not aware of any clinical study that could be used to accurately describe the true impact of such a switch programme in terms of cost savings or clinical benefit for the patient. However, Robinson *et al* (2013) demonstrated that stable, adherent patients prescribed Asacol MR formulations had a 3.5 times higher risk of experiencing a flare when switched to another mesalazine product compared with being maintained on Asacol.

The Panel noted that the table at issue compared the daily and annual costs of Octasa MR 400mg, Octasa MR 800mg and Asacol MR all at 2.4g/day

and stated the annual cost savings per patient and per 300 patients if Octasa was prescribed instead of Asacol. The daily cost for Asacol was stated to be £1.96 with an annual cost of £715.40. The Panel noted that data from Tillotts showed that 120 Asacol MR 400mg tablets cost £39.21 ie 196.05 pence per dose of 2.4g which gave an annual cost of £715.58. The Panel noted that the table stated that the annual cost of Asacol 2.4g/day was £715.40 which was not so. The Panel considered that the table was not accurate in that regard as alleged and a breach of the Code was ruled.

The Panel noted that the table stated the annual cost savings per 300 patients if they were prescribed Octasa 2.4g/day instead of Asacol 2.4g/day. The authors had stated that 300 was the typical number of patients for an average PCT, based on a population of 300,000 and an estimated prevalence of ulcerative colitis of between 120 and 150 per 100,000. The Panel noted that this would therefore mean that an average PCT would have 360 to 450 ulcerative colitis patients.

The Panel noted that Tillotts had stated that the prevalence of ulcerative colitis was 240 per 100,000 population and so an average PCT with 350,000 people would have 840 ulcerative colitis patients. Ninety per cent of those patients would be on mesalazine (756) and at least half of them (378) would be on Asacol given its market share.

The Panel thus noted that the authors' justification for assuming 300 patients and Tillotts' justification for the same were quite different. In that regard the Panel considered that the assumptions made in the table were unclear and in that regard the comparisons made within the table were misleading and the data within the table could not be substantiated. Breaches of the Code were ruled.

The Panel noted that Robinson *et al* post-dated the preparation date of the educational update (December 2012). Robinson *et al*, however, was a retrospective study using a UK pharmacy dispensing database. Although the authors referred to a 3.5 times greater risk of relapse in adherent patients switched from one mesalazine product to another, compared with non-switch patients, the authors stated that further research was needed before making firm conclusions about the implications of the results for disease management. The Panel noted that there was no clinical data before it which showed that patients switched from one mesalazine to another were more likely to experience a flare in their condition as alleged. On that very narrow basis, the Panel considered that the data in table 1 was not misleading in that regard. No breach of the Code was ruled.

Warner Chilcott noted that the paragraph entitled, 'Are there any cost differences?' essentially summarised the data presented in table 1 and included claims that 'Asacol MR is 50% more expensive than Mesren/Octasa MR 400mg and 25% more expensive than Octasa MR 800mg' and that 'One year of maintenance therapy (2.4g daily) would equate to a £72,000 difference in expenditure for 300 patients'. For all the reasons

discussed above Warner Chilcott alleged that these claims were misleading, presented inaccurate and inappropriate cost comparisons and were incapable of substantiation.

The Panel noted that the section of the educational update at issue was a description and justification of the data used in the table considered above. Readers were referred to the table. The Panel noted its comments and rulings above and considered that they applied to the paragraph now at issue. Breaches of the Code were ruled.

Warner Chilcott noted that the concluding paragraph of the supplement contained the claim that 'Octasa MR... represents the least expensive, pH-dependent, modified-release mesalazine product available in the UK'. As indicated above, even with a cost minimisation approach, which might be questionable with no head-to-head clinical data for any mesalazine vs Octasa, claims about the acquisition cost of mesalazine therapy should take into consideration the daily mesalazine dosage which varied by product and indication. Using the recommended dosing schedules and the prices presented in MIMS it was clear that there were mesalazine products/doses available in the UK with a lower acquisition cost than some daily doses of Octasa, including pH-dependent, modified-release tablets. Thus, this claim was alleged to be inaccurate, misleading and incapable of substantiation.

The Panel noted its comments above and considered that they applied here. Breaches of the Code were ruled.

Warner Chilcott submitted that Tillotts' close involvement in the writing, review and approval of this item and in the provision of data to the authors should have assured that the highest standards of content would be maintained. Instead there were a number of fundamental inaccuracies and breaches of the Code which collectively reflected failure to maintain high standards.

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

Warner Chilcott was concerned that the multiplicity of fundamental errors and breaches of the Code contained within the supplement potentially put ulcerative colitis patients at risk. A breach of Clause 2 was alleged.

The Panel noted its rulings above and that some of the matters considered overlapped. Although concerned about the poor standard of the material at issue, the Panel did not consider that it was such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.

Warner Chilcott UK Ltd complained about the promotion of Octasa (mesalazine modified-release tablets) by Tillotts Pharma UK Ltd. The material at issue was a journal supplement (ref UK/OC/0001/0113) published in the British Journal of Clinical Pharmacy. Tillotts submitted that it had

already agreed to refrain from citing the journal supplement as a reference. The journal supplement had been used with health professionals involved in medicines budget management.

Warner Chilcott marketed Asacol (mesalazine modified release).

1 Disguised promotion

COMPLAINT

Warner Chilcott submitted that the supplement looked like a non-promotional, educational update – as indicated by its title ‘Educational update’ – produced by two independent health professionals and formatted in the house style of the British Journal of Clinical Pharmacy. These features were not consistent with the supplement being a promotional item. The Code was explicit on this point and clearly indicated that promotional material in journals should not resemble independent editorial matter. Warner Chilcott alleged a breach of Clause 12.1.

RESPONSE

Tillotts strongly disagreed that the educational update was disguised promotion.

Tillotts submitted that it did not pay for the authorship or publication of the educational update. Tillotts had not had editorial control over the content but had provided data and had been involved in the editorial process, which was clearly stated on the front cover and at the end of the update.

Although the educational update was not written as a promotional piece, it supported the use of Octasa and as such had been offered and provided by Tillotts to support the argument for using Octasa MR 400mg as a lower cost substitute for Asacol MR 400mg. This use of the educational update by Tillotts was promotional.

Tillotts aimed to adhere to the Code and so it ensured that its involvement was clearly and unambiguously stated in the declaration on the front cover; it provided a job bag number and prescribing information. These additions, in line with good practice, demonstrated Tillotts’ involvement and prevented the supplement being considered disguised promotion.

The house style layout and design used in the update was consistent with other articles recently published in the same journal. These articles bore a similar declaration. There was no intention to disguise this.

Tillotts noted that this document was an update to Grosso *et al* (2009) published in the same journal. Tillotts was not involved in the production or compilation of the original article.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even

if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm’s length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The journal supplement in question was written in conjunction with Tillotts; the company had provided data and reviewed and approved the article. The supplement was entitled ‘Introducing Octasa MR (mesalazine) – The lowest cost, oral, pH-dependent, modified-release mesalazine formulation available?’. Prescribing information for Octasa was included on page 4 of the supplement. The Panel considered that Tillotts was inextricably linked to the production of the supplement, there was no arm’s length arrangement. Further, the company had submitted that it had provided reprints of the supplement to support its product, Octasa, vs Asacol and had cited it as a reference in materials. In the Panel’s view, Tillotts was thus responsible under the Code for the content of the supplement.

The front cover of the supplement was headed ‘Educational update’ which was underlined in red. The names of two independent authors appeared in the middle of the front cover. The outside top corner of each page of the article which made up the supplement, featured a red box labeled ‘Educational update’ in bold white type. The Panel noted that a declaration of sponsorship appeared at the bottom of the cover page and again at the end of the article on page 3; the prescribing information for Octasa appeared on page 4.

The Panel noted Tillotts’ involvement with the material and considered that although there were elements to show that the supplement was a promotional piece, its prominent characterisation as an ‘Educational update’ was such that the promotional nature of the material was disguised. In this regard, the Panel further noted Warner Chilcott’s submission that the supplement was formatted in the house style of the journal. Although the Panel had not been provided with a copy of The British Journal of Clinical Pharmacy, it noted that Grosso *et al*, previously published in the same journal, had a similar three column layout and heading structure. A breach of Clause 12.1 was ruled.

2 Declaration of sponsorship

COMPLAINT

Warner Chilcott acknowledged that a declaration of sponsorship was present, but considered that its font size was disproportionately small and the reader could easily miss it at the foot of the first page. Even if this declaration was read, claims for Octasa had already been made earlier on the page. The Code stated that the declaration of sponsorship must be sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset. Given the size and location of the declaration, Warner Chilcott alleged a breach of Clause 9.10.

RESPONSE

Tillotts disagreed. As stated above the declaration was clear and of appropriate prominence on the front cover and consistent with the publisher's own standards for similar declarations in the same journal. In Tillotts' view, the declaration highlighted its involvement and was not in breach of Clause 9.10.

Tillotts submitted that the declaration was appropriately sized, in a prominent position and occupied 20% of the cover depth and the full width. The declaration was in a clear font and of a size that could be read without difficulty under normal circumstances. The declaration stated:

'This educational update was written in conjunction with Tillotts Pharmaceuticals. Tillotts Pharmaceuticals provided no funding to the authors for the creation of this article but have provided data and reviewed and approved the article. Final editorial control rested with the Journal. Prescribing information can be found on page 4. Date of preparation: December 2012 UK/OC/001/0113.'

In addition there was a clear acknowledgement on page 3 at the end of the educational update, in consistent text size with the body text of the update, that stated:

'This educational update was written in conjunction with Tillotts Pharmaceuticals. Tillotts Pharmaceuticals provided no funding to the authors for the creation of this article but have provided data and reviewed and approved the article. Final editorial control rested with the Journal.'

Tillotts submitted that this reiterated its involvement. Therefore there were clear declarations, at both the start and the end of the educational update. Tillotts denied a breach of Clause 9.10.

PANEL RULING

The Panel noted that Clause 9.10 required companies to include a declaration of sponsorship on, *inter alia*, all materials relating to medicines and their uses. The supplementary information stated that the declaration of sponsorship must be sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset.

The Panel noted that Tillotts' declaration of sponsorship appeared on the front cover of the supplement and again at the end of the article. The declaration on the front cover was at the bottom of the page in small white type (a lower case 'm' was less than 2mm high) on a dark grey background. The dark grey band at the bottom of the page occupied 22% of the cover depth; the declaration of sponsorship statement within that band only occupied 5% of the cover depth, not 20% of it as submitted by Tillotts. The declaration statement was below larger type, on the same dark grey background, which referred to the associated journal. All other text on the cover was similarly in bigger and/or bolder type. The prominence of the heading 'Educational update', the title of the article and the author's names and affiliations was emphasized by the bold white type

in which they were written appearing on a black background. The red underlining of 'Educational update' kept the reader's eye to the top or middle of the page. In the Panel's view, the declaration of sponsorship was such that the reader's eye would not be drawn to what appeared to be 'the small print' at the bottom of the page. In that regard the Panel did not consider that the statement was sufficiently prominent to ensure that readers were aware of it at the outset. A breach of Clause 9.10 was ruled.

3 Claim 'Introducing Octasa MR (mesalazine) – The lowest cost, oral, pH-dependent, modified-release mesalazine formulation available?'

This claim appeared as the title of the supplement and of the article.

COMPLAINT

Warner Chilcott noted the question mark at the end of the title but considered that this did not alter the nature of this wording, ie it was a claim for Octasa MR. Although no direct attempt to substantiate this claim was made, the reader was introduced in the first paragraph of the article to a list of available modified-release mesalazine products. No cost data were presented for these products yet the title implied that Octasa was the cheapest option available in this list of seven products.

However, even if taking a cost minimisation approach, which might be questionable with no head-to-head clinical data for any of these products vs Octasa, the acquisition cost of mesalazine therapy should also take into consideration the prescribed daily dosage of mesalazine which varied by product and indication. Using the recommended dosing schedules and the prices presented in MIMS, May 2013, it was clear that there were mesalazine products/doses available in the UK with a lower acquisition cost than some daily doses of Octasa, including pH-dependent, modified release tablets.

Furthermore, this claim implied that both Octasa preparations were equivalently priced, which was not so. Indeed, as shown in table 1 of the item, the daily cost of 2.4g/day mesalazine was greater for Octasa MR 800mg tablets than for Octasa MR 400mg tablets. Clearly both Octasa products could not be the lowest cost formulation available as one was more expensive than the other. Thus, to make a broad claim that Octasa MR was the lowest cost, oral, pH-dependent, modified-release mesalazine formulation available was inaccurate, misleading and incapable of substantiation and in breach of Clauses 7.2 and 7.4.

RESPONSE

Tillotts disagreed that the educational update was in breach of Clauses 7.2 and 7.4 of the Code. The information, claims and comparisons were accurate and not misleading, and could be substantiated.

The question mark in the title clarified the purpose of the preceding words and raised debate around the topic. Questions were intended to raise debate and discussion. It was a question both pertinent to the

timing of the publication, and relevant to the content of the educational update. The update set out to answer the question.

As stated to Warner Chilcott, Octasa was the lowest cost, pH-dependent formulation dose-for-dose. Tillotts was unsure why Warner Chilcott deemed this not to be the case and would have welcomed further communication on the matter.

Tillotts noted that under the European Medicines Evaluation Agency (EMA) guidelines for production of generic medicines, two medicines which contained the same active substance were considered bioequivalent if they were pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lay within acceptable predefined limits. These limits were set to ensure comparable in vivo performance, ie similarity in terms of safety and efficacy.

Tillotts noted that the Asacol patent expired in 2002, since then there had been a generic alternative (Mesren). The original application was submitted by Norton Healthcare to the Medicines and Healthcare Products Regulatory Agency (MHRA) for approval of Mesren MR 400mg tablets. This was a bibliographical application (art 4.8(a)(ii) of Directive 65/65/EC as amended), which permitted the applicant to refer to published scientific literature to show that the constituents of the medicine had a well-established medicinal use with recognized efficacy, and an acceptable level of safety. There was no requirement to include the results of clinical trials in accordance with the second paragraph of Article 1 of Directive 75/318/EEC. Therefore, a direct head-to-head efficacy study between the innovator and generic product was not required.

Both Asacol MR 400mg and Mesren/Octasa MR 400mg contained the same amount of mesalazine and shared the same excipients. Specific differences in terminology and nomenclature were due to the differences in the regulatory bodies (EU for Mesren/Octasa and Food and Drug Administration (FDA) for Asacol).

Mesren/Octasa MR 400mg	Asacol MR 400mg
Lactose	Lactose
Sodium starch glycolate	Sodium starch glycolate
Magnesium stearate	Magnesium stearate
Talc	Talc
Povidone E1201 (polyvinylpyrrolidone)	polyvinylpyrrolidone
Eudragit S (methyl methacrylate copolymer (1:2))	Eudragit S
Dibutyl phthalate	Dibutyl phthalate
Iron Oxides (E172)	Iron Oxides (E172)
Macrogol 6000 (Polyethylene glycol)	Polyethylene glycol

Note: Macrogol 6000 is the International Non-proprietary Name (INN) for polyethylene glycol.

Following MHRA grant to Norton, the licence for Mesren MR 400mg tablets was transferred to Teva and then to Tillotts. The regulatory requirements of the change of ownership required only the data which controlled the manufacture of the medicine to be transferred from Norton to Teva, and then Teva to Tillotts. The name of 'Mesren MR 400mg Tablets' was then changed to 'Octasa 400mg MR Tablets' by a variation.

Tillotts submitted that the MHRA was satisfied that head-to-head trials of Asacol and Mesren/Octasa were not required. Sufficient data existed to satisfy the licensing authority that there was comparable safety and efficacy. There was no scientific reason why a patient on Asacol would require a greater or lesser dose of Octasa. It was completely reasonable to forecast that a patient on Asacol would transfer to the same dose and strength of Octasa. As all strengths of Octasa had a lower acquisition price than the comparable Asacol preparations it followed that switching patients from Asacol to Octasa would reduce medicines expenditure in the NHS. Under any analysis, Octasa branded mesalazines were lower in cost than Asacol. Comparing costs between 400mg and 800mg tablets did not alter this fact; a patient on 2.4g of the more expensive Octasa 800mg would cost the NHS less than a patient on 2.4g of Asacol MR 400mg.

Tillotts submitted that Warner Chilcott was misguided in its calculations and for the reasons above Tillotts was not in breach of Clauses 7.2 and 7.4.

In response to a request for further information, Tillotts provided a table of data which showed all of the available mesalazine formulations and used July 2013 MIMS as the data source (Tillotts submitted that the NHS Tariff prices had not changed between March and August 2013).

Tillotts submitted that the data showed:

- The daily cost of acute and maintenance treatments within the licensed dosage range for adults treated with mesalazines
- Octasa 400mg had the lowest daily maintenance treatment cost for all mesalazines (the most frequently prescribed dose) and the lowest annualized treatment cost
- In practical terms Octasa MR 400mg was also the lowest cost acute phase treatment.

Tillotts stated that the educational update specifically focused on Asacol, Mesren, Octasa and Ipocol, all of which were pH-dependent 400mg tablets with comparable release profiles and dosage range. When the focus was on these comparable treatments the data conclusively supported the claim that Octasa 400mg was the lowest cost pH-dependent mesalazine.

Tillotts added that when high strength pH-dependent formulations were compared as a separate sub-category, Octasa MR 800mg was also the lowest cost when comparable daily doses were examined.

PANEL RULING

The Panel noted that the journal supplement was entitled 'Introducing Octasa MR (mesalazine) – The lowest cost, oral, pH-dependent, modified-release mesalazine formulation available?'. In the Panel's view, although the title was presented as a question, readers would assume it was a claim ie that Octasa MR was the lowest cost, oral, pH-dependent, modified-release mesalazine available.

The first paragraph of the article introduced the reader to the seven modified-release mesalazine preparations which were available until the end of 2012 ie Asacol MR, Ipcol, Mesren MR, Mezavant XL, Pentasa, Salofalk and Octasa MR. In that regard the Panel considered that the claim would be seen in the context of these seven medicines ie that Octasa was the lowest cost compared with them all. The Panel noted that the additional data provided by Tillotts detailed the cost of all of the mesalazine products currently available (ie the seven listed above minus Mesren which had been discontinued). With regard to acute treatment with mesalazine, the data provided by Tillotts showed that Octasa MR 400mg tablets (2.4g/day) was the least expensive treatment option. However, for maintenance therapy a dose of Salofalk 1.5g was the least expensive option and Pentasa sachets were also less expensive than Octasa given that the highest maintenance dose of Octasa was 2.4g/day.

The Panel considered that the basis of the claim at issue had not been made abundantly clear in the journal supplement. It was not clear as to which doses were included in the comparison and if the claim related to acute treatment, maintenance treatment or both. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled. The Panel considered that the claim could not be substantiated. A breach of Clause 7.4 was ruled.

4 Statement 'This article describes how the launch of Octasa MR (Tillotts Pharmaceuticals) provides an opportunity to keep costs down without compromising patient care'.

This statement appeared as part of the sub-heading to page 1 of the article.

COMPLAINT

Warner Chilcott stated that in its view, the article neither presented nor referred to any evidence or data relating to the clinical benefits of Octasa in patient care. The supplement discussed the in vitro dissolution characteristics and cost differences between Asacol MR 400mg/800mg tablets and Octasa (Mesren) MR 400mg/800mg tablets. It appeared therefore that the statement 'without compromising patient care' was based purely on the extrapolation of in vitro data to the clinical situation and implied that without clinical evidence, the products discussed could be simply interchanged without affecting patient management or compromising patient care. To make this assumption without clinical data to show that it was of direct relevance and significance was misleading, in breach of Clause 7.2.

RESPONSE

Tillotts submitted that Warner Chilcott had taken the statement out of the context of the article to create a complaint. The article actually stated 'The discontinuation of Mesren MR (mesalazine; Teva Pharmaceuticals) could have considerable cost implications for the NHS. This article describes how the launch of Octasa MR (Tillotts Pharmaceuticals) provides an opportunity to keep costs down without compromising patient care'. As explained above, Octasa MR 400mg was Mesren rebranded following the transfer of the marketing authorization to Tillotts. Therefore it could be fairly assumed that keeping patients on exactly the same formulation/medicine would not compromise care.

Tillotts submitted that Warner Chilcott wanted to transfer patients from Mesren to Asacol as demonstrated in its recent advertising. The allegation of a breach of Clause 7.2 was unsupportable on the basis that Octasa MR 400mg, and Mesren MR 400mg contained exactly the same active ingredient, excipients and had the same coating and release profile (they were the same product with a change of name). These medicines were interchangeable.

There was over 10 years of experience with Mesren in the UK. A proportion of these patients were initiated on Asacol in secondary care and transferred in primary care to Mesren. There was no evidence that transferring patients from Asacol to Mesren caused any additional risk to the patients' health.

Tillotts reiterated that Norton Healthcare was originally granted a licence for the product in 2002, this was transferred to Teva (when Teva acquired Norton Healthcare) and subsequently, in 2012, the licence was transferred to Tillotts. The transfer of the licence to Tillotts also included a brand name change from Mesren to Octasa. It was clear therefore that all patients who had previously taken Mesren should be transferred to Octasa as it was the same medicine and in doing so the cost to the NHS would be kept down, because there would be 50% increase in costs to the NHS if these patients migrated to Asacol.

Tillotts denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the statement at issue was the second sentence to the subheading on page 1 of the article. The sub-heading, in full, read:

'The discontinuation of Mesren MR (mesalazine' Teva Pharmaceuticals) could have considerable cost implications for the NHS. This article describes how the launch of Octasa MR (Tillotts Pharmaceuticals) provides an opportunity to keep costs down without compromising patient care.'

The Panel noted that with the discontinuation of Mesren, patients previously taking that medicine would have to be switched to an alternative mesalazine product. The Panel further noted that Octasa was, as stated in the article, essentially a rebrand of Mesren; the formulation of both medicines was the same. In the Panel's view,

patients switching from Mesren to Octasa should not notice a clinical difference in therapy.

The Panel considered that in the context of the discontinuation of Mesren MR, the statement at issue was not misleading as alleged. No breach of Clause 7.2 was ruled.

5 Disregard of current guidelines and recommendations on prescribing modified-release mesalazine

COMPLAINT

Warner Chilcott submitted that whilst the supplement referred to the British Society of Gastroenterology (BSG), the European Crohn's and Colitis Organisation (ECCO) and the British National Formulary (BNF) guidelines and statements, it was quick to disregard the caution represented by these respected national and international bodies in relation to indiscriminate switching between mesalazine brands and the recommendation to prescribe modified-release mesalazine by brand. To date, there had been no head-to-head clinical studies between Octasa and any other mesalazine and very few head-to-head clinical studies between the different modified-release mesalazines in general. Absence of evidence showing clinical differences between mesalazines (because these studies had not been conducted) was not equivalent to evidence demonstrating no clinically significant differences between the mesalazines, hence the appropriate caution in the guidelines that these products should not be considered interchangeable. To dismiss these cautions and recommendations clearly supported Tillotts' promotional drive to have patients receiving other mesalazines indiscriminately switched to Octasa. Dismissal and misrepresentation of the guidelines in this way was misleading and did not encourage the rational use of Octasa.

Furthermore, Warner Chilcott noted the comment that the BNF statement was 'originally made before the introduction of Mesren MR 400mg and Octasa MR 400mg to the UK market'. Whilst that might or might not be true (Mesren MR 400mg tablets were first licensed in the UK in November 2003) the comment implied that the BNF's position was outdated and could be further disregarded on these grounds. Warner Chilcott noted that the hard copy BNF was updated every six months and the digital version, every month. As the BNF continued to use this statement, it presumably reflected the BNF's current position and was not an outdated recommendation as implied.

Warner Chilcott alleged that this section of the supplement misled by distortion and failed to encourage the rational use of Octasa, in breach of Clauses 7.2 and 7.10.

RESPONSE

Tillotts strongly disagreed that the educational update breached Clauses 7.2 or 7.10. The company considered that the information provided was not misleading and that it did encourage the rational use of medicines.

Tillotts stated that the basis of the complaint was unclear. The educational update provided balanced, fair and rational evaluations of medicines that shared the same active ingredient, the same excipients and the same delivery profile; it did not advocate indiscriminate switching. The article specifically stated, 'This review will focus on Mesren MR 400mg, Octasa MR 400mg and Asacol MR 400mg, since other modified-release mesalazine preparations have marked differences in delivery characteristics', the review was therefore very discriminate and was focused entirely on these three medicines which, as already established, shared the same delivery profiles, delivery systems, excipients and active ingredients. As stated in inter-company dialogue, none of the guidelines referred to by Warner Chilcott made such a caution in relation to 'indiscriminate' switching.

The BSG and ECCO guidelines were accurately quoted within the educational update. The reader was alerted to these guidelines and relevant extracts quoted from these respected guidelines. The article did not disregard the guidelines but firmly supported their recommendations. The educational update also quoted the BNF guidance 'The delivery characteristics of oral mesalazine preparations may vary; these preparations should not be considered interchangeable'. In the case of Mesren/Octasa MR 400mg and Asacol MR 400mg the delivery characteristics did not vary, this was specifically discussed and demonstrated by the two graphs showing comparative dissolution profiles. The article specifically asked the reader to consider very discriminate brand switching in alignment with the established guidelines. Further, it was the purpose of this type of journal to challenge readers to update their own knowledge and consider whether guidance that their organizations currently provided was fully informed such as including cost as one of their decision-making criteria when considering oral, pH-dependent mesalazine.

The educational update stated that the BNF guidelines were written before Mesren was introduced, this was factually correct. The BNF guidance had not changed since it was introduced, despite new brands entering the market, however as stated above its intention was to guide prescribers away from switching patients between mesalazines with differing delivery characteristics, unlike Mesren/Octasa MR 400mg and Asacol MR 400mg which shared the same dissolution profiles and therefore delivery characteristics.

PANEL RULING

The Panel noted that the first section of the journal supplement introduced the reader to seven modified release mesalazine preparations and then stated that the article would describe some of the similarities and differences of three of them – Mesren, Octasa and Asacol. The next section of the article referred to prescribing guidelines and that the BSG and ECCO had recommended that modified-release mesalazine should be prescribed by brand. It was stated however, that both guidelines appeared to suggest that there was little in the way of significant differences between available products with regard

to important clinical outcomes. It was noted that the BNF statement which advised that oral mesalazine preparations should not be considered interchangeable was made before Mesren and Octasa had been introduced to the UK market.

The Panel considered that overall, the take home message was that it was not important to prescribe any modified-release mesalazine by brand and that they were all essentially interchangeable. In that regard the Panel noted that the sub-heading referred to 'modified release mesalazine' and so it appeared that the subsequent discussion was not restricted in its scope to Asacol, Mesren and Octasa. The Panel considered that this was misleading. A breach of Clause 7.2 was ruled. The Panel did not consider that the information encouraged the rational use of Octasa. A breach of Clause 7.10 was ruled.

6 Paragraph entitled 'Are there any significant differences between Asacol MR and Octasa MR?'

COMPLAINT

Warner Chilcott noted that although the supplement conceded that Octasa had not been compared directly with Asacol MR in a clinical setting, no clinical efficacy or safety data for either Octasa or Asacol was presented. Clearly, the consideration of clinical evidence should be fundamental to any comparative evaluation of two products. Instead, the article focussed on data from in vitro dissolution studies to make a case for (clinical) similarity between Asacol and Octasa.

However, the methodology of these in vitro studies made it impossible to draw any meaningful conclusions about the similarities or differences between these products in vivo, *let alone* in various stages of disease activity in patients with ulcerative colitis. Presenting dissolution data in isolation was problematic, as in vitro dissolution studies could not fully reproduce the conditions of the gastrointestinal tract in patients with ulcerative colitis. Furthermore, no statistical comparisons between the findings for Mesren and Asacol were presented and no in vitro/in vivo correlation had been established to indicate the potential clinical significance of the findings. Warner Chilcott noted that Fadda and Basit (2005), presented in the supplement even commented on the poor in vitro/in vivo correlations obtained for pH-responsive, modified-release dosage forms. Thus, any conclusions about the significance of the findings of these in vitro data were impossible and attempting to do so in this manner alleged to be misleading in breach of Clause 7.2.

RESPONSE

Tillotts submitted that as already stated, Mesren/Octasa MR 400mg was a generic copy of Asacol MR 400mg which lost its patent protection in 2002. Tillotts was the originator of Asacol MR and continued to manufacture and distribute 400mg modified-release mesalazine in 55 countries worldwide with over 1.5 million patients-years' experience with this formulation, showing that it

was well tolerated and effective. Warner Chilcott currently manufactured Asacol MR 400mg to the same formulation as that originally developed and marketed by Tillotts in the UK. This same formulation was used by Tillotts to manufacture Octasa MR 400mg in the UK (Tillotts noted that in the UK the brand name Asacol was the commercial property of Warner Chilcott). Tillotts however continued to manufacture and market its mesalazine product as Asacol MR 400mg for markets outside the UK. The question asked by the authors was completely valid.

Tillotts submitted that head-to-head studies were deemed unnecessary by the MHRA when Mesren was approved, as Mesren (Octasa MR 400mg) and Asacol MR 400mg were pharmaceutically equivalent. Dissolution data presented to pharmacists familiar with these analyses, supported this point, and showed no significant differences in dissolution.

Tillotts denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that in the section of the supplement entitled 'Are there any significant differences between Asacol MR and Octasa MR?' it was clearly stated that 'Octasa MR has not been compared directly in a clinical study with Asacol MR'. The relevant section reported that Fadda and Basit had shown that Mesren and Asacol had similar dissolution profiles and that a more recent study carried out by Tillotts showed very little difference in the dissolution profiles of the two products.

The Panel noted that the section at issue focussed on in vitro dissolution data. The supplementary information to Clause 7.2 of the Code stated that care should be taken with the use of in vitro data and the like so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance.

The Panel noted that the first sentence of the section at issue stated that there had been no clinical comparison of Asacol MR and Octasa MR. The Panel further considered that most readers would read the rest of the section and assume, even in the acknowledged absence of clinical data, that because the in vitro dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to show that this was so. The Panel considered that the supplement was misleading in this regard. A breach of Clause 7.2 was ruled.

7 Graph not fully labelled

COMPLAINT

Warner Chilcott noted that the y-axis of the graph at figure 2 was unlabelled and so it was unclear and ambiguous as to what was presented. Failing to label the graph made it impossible for the reader to interpret the findings presented. As this graph represented data on file provided by Tillotts, Warner

Chilcott alleged that Tillotts had thus failed to maintain high standards in terms of representing its own data and reviewing the article before publication in breach of Clauses 7.2 and 9.1.

RESPONSE

Tillotts acknowledged that the y-axis was not labelled on figure 2: 'Dissolution of Mesren MR 400mg vs Asacol MR 400mg and 800mg', but denied a breach of Clauses 7.2 and 9.1.

Tillotts submitted that figures 1 and 2 were laid out side by side and the label of the y-axis of figure 1 could be applied to both graphs. The pages faced each other and readers were able to read across the page to review the two graphs side by side. However in order to increase the clarity of this item Tillotts submitted that it had contacted the editor of the British Journal of Clinical Pharmacy and suggested that a label be added to the y-axis of figure 2. Tillotts had also withdrawn reprints of the article from use and would only use them again if and when the omission was corrected.

Tillotts did not consider that the omission of the label rendered the figure misleading and it therefore denied a breach of Clause 7.2.

Tillotts also did not consider that the omission constituted a breach of Clause 9.1. Any potential reduction in clarity from this single omission was minor and was not misleading. It therefore did not represent a failure to maintain high standards of the order of magnitude referred to in the Code (eg causing offence).

PANEL RULING

The Panel noted that the graph was referenced to 'Tillotts Pharma 2012. Data on file' and headed 'Dissolution of Mesren MR 400mg vs Asacol Mr 400mg and 800mg'. The y-axis was not labelled and so in that regard the Panel considered that the graph did not reflect the evidence clearly. In the Panel's view it was immaterial that the graph was next to another similar graph which did have the y-axis labelled; each graph should be capable of standing alone. The Panel ruled a breach of Clause 7.2. The Panel further considered that the use of a poorly labelled graph meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

8 Cost comparison data

COMPLAINT

Warner Chilcott alleged that the figure presented for the annual cost of Asacol, 2.4g/day, should be £715.58 and not £715.40 as shown. This error meant that all data presented in rows three and four of the table (which included the incorrect figure for Asacol in its calculation) were also inaccurate. Warner Chilcott alleged a breach of Clause 7.2.

Warner Chilcott further submitted that the table was misleading in that if a patient failed to respond to Asacol or Octasa at a dose of 2.4g/day they would

not be maintained on that dose for 365 days of the year; the dose would either be increased to 4.8g/day in the case of patients with moderately active ulcerative colitis until symptoms were brought under control (typically 6-8 weeks) or be prescribed other medicines such as corticosteroids. Further, if patients responded to treatment with 2.4g/day, once symptoms were quiescent the dose of Asacol/Octasa was likely to be reduced for the maintenance of remission of ulcerative colitis. Failure to take this into account in the costs therefore presented an artificial and misleading scenario that would not be encountered in clinical practice and therefore this table presented inflated and unrealistic cost savings that could never be achieved.

Warner Chilcott further submitted that the table failed to inform the reader that to obtain the proposed cost savings, the calculations assumed that all 300 patients (the typical number of patients with ulcerative colitis in an average primary care trust (PCT)) would be switched from Asacol to Octasa. This was simply not the case. Even though Asacol was the acknowledged market leader, it had only approximately 40% of market share. As this had not been taken into account, the figures proposed were additionally inflated and misleading.

Other factors omitted from the calculations presented in table 1 were the cost of implementing such a switch and the management of any negative clinical impacts that the switch might have e.g. risk of relapse or other adverse event. Warner Chilcott was not aware of any clinical study that could be used to accurately describe the true impact of such a switch programme in terms of cost savings or clinical benefit for the patient. However, the potential impact of switching stable adherent patients between formulations was considered by Robinson *et al* (2013) who demonstrated that stable adherent patients prescribed Asacol MR formulations had a 3.5 times higher risk of experiencing a flare when switched to another mesalazine product compared with being maintained on Asacol.

Warner Chilcott therefore alleged that table 1 was misleading, presented inaccurate and inappropriate cost comparisons and was not capable of substantiation in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Tillotts strongly disagreed that the educational update breached Clauses 7.2, 7.3 and 7.4; the information provided and comparisons made were not misleading and could be substantiated.

Tillotts submitted that the assumptions used in the calculations were clearly stated. Warner Chilcott considered that the authors' calculations were inaccurate in that the annual cost of Asacol should be £715.58 rather than £715.40 as stated (a difference of 18 pence). Tillotts was unsure as to how Warner Chilcott got to its figure as the stated daily cost of Asacol was £1.96 based on 2.4g/day. If this cost was multiplied by 365 days (as stated in the table) then the annual cost was £715.40 as stated ie $£1.96 \times 365 = £715.40$. Tillotts stated that it would have

welcomed further discussions with Warner Chilcott if it had raised this difference.

Tillotts stated that all assumptions used in the calculations had been clearly stated by the authors. For the purposes of health economic modelling and forecasting certain assumptions had to be made, in the educational update a fair assumption was made that the number of patients on less than 2.4g/day would be counter balanced by the number of patients on more than 2.4g/day, as patients might increase their dose to 4.8g/day during a flare of ulcerative colitis. Approximately 70% of patients with ulcerative colitis who took mesalazines remained in remission each year, patients who relapsed might be treated by doubling the dose to 4.8g/day, which would double the cost. Whereas, if patients took 1.6g/day this would reduce the cost by 33%. A mean of 2.4g/day (which was clearly stated) was a fair and reasonable assumption on which to model. This was not misleading and therefore not in breach of Clause 7.2, 7.3 or 7.4.

The figures shown in table 1 were transparent. The difference in cost between 365 days' treatment with Asacol vs Octasa was a cost reduction of £240.90/patient treated with Octasa, which for 300 patients would amount to £72,270. The difference in cost between patients taking 2.4g/day of Asacol 400 vs Octasa 800 was lower at a daily difference of £1.58 and annualized in 300 patients to £41,244.

A population of 300 patients on Asacol was selected as typical for a PCT on the basis that ulcerative colitis had a prevalence of approximately 240 per 100,000 of the population in the UK (NICE CG166 guidelines). A typical PCT had a population of around 350,000, hence it would typically have 840 ulcerative colitis patients. The vast majority of these patients would be treated with a mesalazine first line, they might or might not have steroids and/or other topical forms of mesalazine included in their treatment regimens. However, it was assumed that the 'other therapies' remained constant and were not affected. The figures discussed in the educational update were the costs of treating patients with Asacol or Octasa only. If 90% of the treated population were on a mesalazine (which was a fair assumption), 756 patients would be on an oral mesalazine. When the educational update was published, Asacol had a market share in excess of 50% (IMS RSA data December 2012 51.17%), this would be approximately 378 patients per typical PCT. This meant that the estimates which were discussed in the educational update were conservative.

Tillotts noted Warner Chilcott's suggestion that switching patients might cause patient to flare but stated that there was no trial evidence to support this statement.

The cost savings achieved by Surrey PCT and discussed in the educational update had been realized through a programme managed by the author, a medicines management pharmacist with that PCT.

PANEL RULING

The Panel noted that the table at issue compared the daily and annual costs of Octasa MR 400mg, Octasa MR 800mg and Asacol MR all at 2.4g/day and stated the annual cost savings per patient and per 300 patients if Octasa was prescribed instead of Asacol. The daily cost for Asacol was stated to be £1.96 with an annual cost of £715.40. The Panel noted that data from Tillotts showed that 120 Asacol MR 400mg tablets cost £39.21 ie 196.05 pence per dose of 2.4g which gave an annual cost of £715.58. The Panel noted that the table stated that the annual cost of Asacol 2.4g/day was £715.40 which was not so. The Panel considered that the table was not accurate in that regard as alleged and a breach of Clause 7.2 was ruled.

The Panel noted that the table stated the annual cost savings per 300 patients if they were prescribed Octasa 2.4g/day instead of Asacol 2.4g/day. The authors had stated that 300 was the typical number of patients for an average PCT, based on a population of 300,000 and an estimated prevalence of ulcerative colitis of between 120 and 150 per 100,000. The Panel noted that this would therefore mean that an average PCT would have 360 to 450 ulcerative colitis patients.

The Panel noted that Tillotts had stated that the prevalence of ulcerative colitis was 240 per 100,000 population and so an average PCT with 350,000 people would have 840 ulcerative colitis patients. Ninety per cent of those patients would be on mesalazine (756) and at least half of them (378) would be on Asacol given its market share.

The Panel thus noted that the authors' justification for assuming 300 patients and Tillotts' justification for the same were quite different. In that regard the Panel did not consider that the assumptions made in the table were clear and in that regard the comparisons made within the table were misleading in breach of Clauses 7.2 and 7.3. The Panel considered that the data within the table could not be substantiated. A breach of Clause 7.4 was ruled. The Panel noted that Robinson *et al* post-dated the preparation date of the educational update (December 2012). Robinson *et al*, however, was a retrospective study using a UK pharmacy dispensing database. Although the authors referred to a 3.5 times greater risk of relapse in adherent patients switched from one mesalazine product to another, compared with non-switch patients, the authors stated that further research was needed before making firm conclusions about the implications of the results for disease management. The Panel noted that there was no clinical data before it which showed that patients switched from one mesalazine to another were more likely to experience a flare in their condition as alleged. On that very narrow basis, the Panel considered that the data in table 1 was not misleading in that regard. No breach of Clause 7.2 was ruled.

9 Paragraph entitled, 'Are there any cost differences?'

COMPLAINT

Warner Chilcott submitted that this paragraph essentially summarised the data presented in table 1 and included claims that 'Asacol MR is 50% more expensive than Mesren/Octasa MR 400mg and 25% more expensive than Octasa MR 800mg' and that 'One year of maintenance therapy (2.4g daily) would equate to a £72,000 difference in expenditure for 300 patients'. For all the reasons discussed in Point 8 above Warner Chilcott alleged that these claims were misleading, presented inaccurate and inappropriate cost comparisons and were incapable of substantiation in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Tillotts disagreed for the reasons stated in Point 8 above.

PANEL RULING

The Panel noted that the section of the educational update at issue was a description and justification of the data used in table 1 considered at Point 8 above. Readers were referred to table 1. The Panel noted its comments and rulings above and considered that they applied to the paragraph now at issue. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

10 'Octasa MR ... represents the least expensive, pH-dependent, modified-release mesalazine product available in the UK'

COMPLAINT

Warner Chilcott noted that the concluding paragraph of the supplement contained the claim that 'Octasa MR... represents the least expensive, pH-dependent, modified-release mesalazine product available in the UK'. As indicated in Point 3 above, even with a cost minimisation approach, which might be questionable with no head-to-head clinical data for any other mesalazine vs Octasa, claims about the acquisition cost of mesalazine therapy should also take into consideration the daily dosage (which varied by product and indication) of mesalazine that the patient was prescribed. Using the recommended dosing schedules and the prices presented in MIMS it was clear that there were mesalazine products/ doses available in the UK with a lower acquisition cost than some daily doses of Octasa, including pH-dependent, modified-release tablets. Thus, this claim was alleged to be inaccurate, misleading and incapable of substantiation and in breach of Clauses 7.2 and 7.4.

RESPONSE

Tillotts strongly disagreed with the complaint and denied any breach of Clauses 7.2 or 7.4. The claim at issue was a statement of fact as addressed in the company's response to Point 3.

The concluding paragraph discussed the brand name change from Mesren to Octasa. Mesren was considered the cheapest pH-dependent, modified-release mesalazine product in the UK but given the name change this was now Octasa MR 400mg. The emphasis of the educational update was a comparison of like-for-like treatments, Mesren/Octasa and Asacol; if patients were switched between Asacol and Octasa there would be a 34% cost reduction for the NHS. Other non-pH-dependent mesalazines on a dose per dose comparison with Octasa MR 400mg were also more expensive than Octasa. Octasa MR 400mg was the lowest cost, oral, pH-dependent mesalazine dose-for-dose. It was unclear as to what Warner Chilcott believed was inaccurate or misleading about this. Tillotts regretted that there had been no opportunity for further inter-company dialogue which might have resolved this.

Head-to-head trials did not exist because Mesren/Octasa was a generic copy of Asacol and head-to-head studies were not required by the MHRA because the formulation of Octasa and Asacol was considered to be sufficiently the same as not to warrant such trials.

The data provided was not misleading and could be substantiated. Tillotts denied a breach of Clauses 7.2 or 7.4.

PANEL RULING

The Panel noted its comments at Point 3 above and considered that they applied here. As at Point 3, the Panel considered that the basis of the claim at issue had not been made abundantly clear. It was not clear as to which doses were included in the comparison and if the claim related to acute treatment, maintenance treatment or both. For maintenance therapy, two preparations were shown to be less expensive than Octasa MR. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled. The Panel considered that the claim could not be substantiated. A breach of Clause 7.4 was ruled.

11 Failure to maintain high standards

COMPLAINT

Warner Chilcott submitted that Tillotts' close involvement in the writing, review and approval of this promotional item and in the provision of data to the authors should have assured that the highest standards of content would be maintained. Instead the item included a number of fundamental inaccuracies and breaches of the Code which should have been identified and corrected by Tillotts during its review. These inaccuracies collectively reflected failure to maintain high standards in breach of Clause 9.1.

RESPONSE

Tillotts strongly disagreed. As stated above, the inaccuracies claimed by Warner Chilcott seem to relate to its calculations rather than the authors'.

The educational update was an independently written and published update produced in the house style of the British Journal of Clinical Pharmacy. The information included in the update was accurate (as mentioned in Point 8) and as such Tillotts denied a breach of Clause 9.1.

PANEL RULING

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

12 Alleged breach of Clause 2

COMPLAINT

Warner Chilcott stated that materials associated with the promotion of prescription only medicines must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. Unfortunately, given the multiplicity of fundamental errors and breaches of the Code contained within the supplement, despite the close involvement of Tillotts in its review and approval, Warner Chilcott was concerned that patients with ulcerative colitis had potentially been put at risk by this item and therefore it alleged a breach of Clause 2.

Warner Chilcott also noted its concerns about the responses that were received via inter-company dialogue which further reduced its confidence in Tillotts' understanding of the Code and resulted

in referral of the matter to the PMCPA in order to secure a timely and appropriate conclusion of this matter, which the company considered might otherwise not have occurred.

RESPONSE

For the reasons given above, and the fact that there were no inaccuracies, Tillotts clearly disagreed with the complaint. Tillotts did not consider that the educational update breached the Code, brought discredit on the industry or undermined patient safety. The educational update was independently written by pharmacists with budgetary responsibilities, for other health professionals (predominantly pharmacists) with budget responsibilities. It raised the question as to whether the NHS should pay more for similar products.

PANEL RULING

The Panel noted its rulings above and that some of the matters considered overlapped. Although concerned about the poor standard of the material at issue, the Panel did not consider that it was such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.

Complaint received

17 June 2013

Case completed

10 September 2013

ANONYMOUS RENAL NURSE v JANSSEN

Durogesic promotional aid

An anonymous, non-contactable, renal nurse complained that Durogesic DTrans (fentanyl trans-dermal patch) branded pens had been included in delegate bags at the British Royal Society (BRS) Meeting in Manchester, 14 to 16 May 2013. Durogesic was marketed by Janssen and was indicated in adults in the management of chronic intractable pain, whether due to cancer or otherwise, and in the long-term management of severe chronic pain in children receiving opioid therapy from 2 years of age.

The detailed response from Janssen is given below.

The Panel noted that in March 2010, an unspecified quantity of the branded pens had been donated to the BRS following a request for practical support from the industry. The Panel assumed that given their subsequent provision in delegate bags, Janssen must have donated a large number of pens and so it was not unreasonable to expect that the pens would be redistributed. The Panel noted Janssen's submission that there was no promotional intent in the supply of the pens to the BRS but considered that given the product logo, they could not be considered as anything other than promotional aids. When they were donated, branded pens were acceptable promotional aids under the 2008 Code. The Panel queried, however, whether the branded pens at issue should have been donated to the BRS at all given Janssen's submission that Durogesic DTrans was not routinely used in renal medicine. In that regard the Panel noted that the current summary of product characteristics recommended that if patients with renal impairment received Durogesic DTrans, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary. The Panel further noted that the 2011 Code (effective from 1 January, 2011 but with a transition period until 30 April, 2011) onwards prohibited the use of branded pens as promotional aids.

The Panel noted that branded pens, donated in 2010 by Janssen to the conference organisers, had been distributed in the delegate bags in 2013. The Panel noted Janssen's submission that it first knew about the provision of the pens on 16 May via another pharmaceutical company. The Panel noted that the conference brochure clearly stated that the pens had been donated by Janssen in 2010 and it queried how Janssen did not apparently see that statement and thus know about the provision of the pens before being alerted to the fact by a third party on the last day of the conference. The Panel noted that the provision of branded pens was no longer acceptable under the Code. A breach of the Code was ruled.

Upon appeal by Janssen the Appeal Board noted that approximately 5,000 pens displaying the Durogesic DTrans product logo had been donated

to in 2010 after a request for practical support. Janssen envisaged that the pens would be used for BRS meetings including the annual conference in 2010 which according to BRS had approximately 1,500 attendees. The company assumed that the pens would be distributed over 2 years including the 2011 annual conference held in the spring. The Appeal Board noted the submission from the BRS that the pens would also have been distributed at smaller meetings. The Appeal Board noted that following the donation in 2010 there had been no further discussion between the parties about the pens. There were other sponsors for its 2011 and 2012 conferences. In the absence of a sponsor in 2013 it unilaterally decided to retrieve the pens from storage for use at its conference.

The Appeal Board noted that prior to the 2011 Code pens with brand names could be distributed to health professionals under that edition of the Code and it considered that the prohibition of such pens introduced in the 2011 Code was not retrospective. However, it did not necessarily agree with Janssen's statement that as the industry had not been required to withdraw items given to individual health professionals the company could not have been expected to withdraw the pens given to an organisation such as the BRS.

The Appeal Board noted that the BRS conference brochure for 2013 stated that the pens had been donated by Janssen in 2010. The Appeal Board noted that the Janssen representative at the 2013 BRS conference had not seen the delegate pack. The Appeal Board was concerned that Janssen had not seen the conference brochure given it had a promotional stand at the conference. The Appeal Board noted that Durogesic was not routinely used in renal patients.

The Appeal Board considered that a large number of pens had been donated in 2010 and these needed to be used by the end of the transition period, ie 30 April 2011. The Appeal Board noted that whilst Janssen had donated the pens to BRS it was not thereby absolved of all responsibility under the Code in relation to their future use. Although it was concerned at the large number donated for redistribution, it considered that given the number of attendees at conferences, it was, on balance, not unreasonable for Janssen to assume that the pens would be redistributed by the BRS within a reasonable period of time such that their provision would not be affected by changes introduced in the 2011 Code. The Appeal Board ruled that there had been no breach of the Code. The appeal on this point was successful.

An anonymous, non-contactable, renal nurse complained that Durogesic DTrans (fentanyl trans-dermal patch) branded pens had been included in

the delegate bags at the BRS Meeting in Manchester, 14 to 16 May 2013. Durogesic was marketed by Janssen and was indicated in adults in the management of chronic intractable pain, whether due to cancer or otherwise, and in the long-term management of severe chronic pain in children receiving opioid therapy from 2 years of age.

COMPLAINT

The complainant was surprised to see Durogesic branded pens in the delegate bags at the recent BRS Meeting. The complainant thought that pharmaceutical companies were no longer allowed to produce branded pens and that it was against the Code to do so.

When writing to Janssen, the Authority asked it to respond in relation to Clause 18.3 of the Code.

RESPONSE

Janssen submitted that based on recollections of employees involved at the time, the pens in question, which incorporated the Durogesic DTrans logo, were last ordered by Janssen in 2007. A photograph of the pen was provided.

An unspecified quantity of pens displaying the product logo had been donated to the BRS in 2010 after BRS requested practical support from pharmaceutical companies. The BRS secretariat believed the pens were received in March. Janssen regarded the pens as surplus to requirement at that time, and although Durogesic DTrans was not routinely used in renal medicine, the pens were considered potentially useful to the BRS. There was no promotional intent in the supply of these pens to the BRS.

Janssen first knew that the pens were in the conference bags on 16 May 2013, when one of its employees at the conference was alerted by an employee of another pharmaceutical company. The Janssen employee immediately spoke to a representative of the BRS secretariat. It was pointed out that the conference brochure contained an acknowledgement that the pens were donated by Janssen in 2010 (the relevant page of the conference brochure was provided). Janssen had not been consulted about this acknowledgement in the conference brochure.

Janssen explained that it had a promotional stand in the exhibition area of the BRS conference which promoted Eprex (epoetin alfa). No pens or other promotional items had been provided at this stand.

Janssen submitted that it had not been consulted about placing the pens in the conference bags for the 2013 BRS conference in Manchester, nor had it given permission for the BRS to do so. The BRS confirmed in a letter to Janssen dated 18 June 2013 that: 'The pens were supplied by Janssen UK in 2010. These remained unused in storage and a decision was made to place them in this year's delegate bags rather than throw them out. The company themselves were not aware this was occurring and

at no time were party to the decision to place these pens in the bags'.

The relevant job-bag, which Janssen assumed had been raised in 2007 when the pens were last ordered, had been destroyed in accordance with its routine records management policy, so it was unable to produce the certificate used to approve the pen.

In summary, Janssen submitted that the pens had been donated to the BRS in 2010 and had been placed in the conference bags by the BRS unbeknown to Janssen. Janssen stated that its actions had at all times been compliant with the Code given the circumstances outlined above and did not believe there had been a breach of Clause 18.3.

PANEL RULING

The Panel noted that in March 2010, an unspecified quantity of the branded pens had been donated to the BRS following a request for practical support from the industry. The Panel assumed that given their subsequent provision in delegate bags, Janssen must have donated a large number of pens and so it was not unreasonable to expect that the BRS would distribute such items to its members. The Panel noted Janssen's submission that there was no promotional intent in the supply of the pens to the BRS but considered that given the product logo, they could not be considered as anything other than promotional aids. When they were donated, branded pens were acceptable promotional aids under the 2008 Code. The Panel queried, however, whether the branded pens at issue should have been donated to the BRS at all given Janssen's submission that Durogesic DTrans was not routinely used in renal medicine. In that regard the Panel noted that the current summary of product characteristics (last revised 14 May 2013), available on the electronic Medicines Compendium website, recommended that if patients with renal impairment received Durogesic DTrans, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary. The Panel further noted that the 2011 Code (effective from 1 January, 2011 but with a transition period until 30 April, 2011) onwards prohibited the use of branded pens as promotional aids.

The Panel noted that branded pens, donated in 2010 by Janssen to the conference organisers, had been distributed in the delegate bags at the BRS meeting in Manchester in 2013. The Panel noted Janssen's submission that it first knew about the provision of the pens on 16 May via a colleague from another pharmaceutical company. In that regard the Panel noted that the conference brochure clearly stated that the pens had been donated by Janssen in 2010 and it queried how Janssen did not apparently see that statement and thus know about the provision of the pens before being alerted to the fact by a third party on the last day of the conference. The Panel noted that the provision of branded pens was no longer acceptable under the Code. A breach of Clause 18.3 was ruled. This ruling was appealed by Janssen.

APPEAL FROM JANSSEN

Janssen submitted that when it donated the branded pens to the BRS in early 2010, the Code in force at that time did not prohibit the provision of such branded items. In that regard the company's actions had been appropriate and consistent with the relevant Code. The ownership and control of the pens passed to the BRS and Janssen played no further role in deciding to what use the pens would be put.

Janssen submitted that the BRS had confirmed in writing that Janssen was not consulted about its decision to place the pens, which it had in storage, in the delegate bags for its conference held in May 2013.

APPEAL BOARD RULING

The Appeal Board noted from the Janssen representatives at the appeal that approximately 5,000 pens displaying the Durogesic DTrans product logo had been donated to the BRS in 2010 after BRS had requested practical support from pharmaceutical companies. Janssen envisaged that the pens would be used for BRS meetings including the annual conference in 2010 which according to BRS had approximately 1,500 attendees. The company assumed that the pens would be distributed over 2 years including the 2011 annual conference held in the spring. The Appeal Board noted the submission that the pens would also have been distributed at smaller meetings. The Appeal Board noted that following the donation in 2010 there had been no further discussion between the BRS and Janssen regarding the pens. The Appeal Board noted that, in response to a question, the BRS submitted that it had other sponsors for its 2011 and 2012 conferences. In the absence of a sponsor in 2013 it unilaterally decided to retrieve the pens from storage for use at its conference.

The Appeal Board noted that prior to the 2011 Code (effective from 1 January, 2011 but with a transition period until 30 April, 2011) pens with brand names

could be distributed to health professionals under that edition of the Code. The Appeal Board considered that the prohibition of such pens introduced in the 2011 Code was not retrospective. However, it did not necessarily agree with Janssen's statement at the appeal hearing that as the industry had not been required to withdraw items given to individual health professionals the company could not have been expected to withdraw the pens given to an organisation such as the BRS.

The Appeal Board noted that the BRS conference brochure for 2013 stated that the pens had been donated by Janssen in 2010. The Appeal Board noted from the Janssen representatives at the appeal that its representative at the 2013 BRS conference had not seen the delegate pack including the brochure as he/she had downloaded the agenda from the internet. The Appeal Board was concerned that Janssen had not seen the conference brochure given it had a promotional stand at the conference. The Appeal Board noted that Durogesic was not routinely used in renal patients.

The Appeal Board considered that a large number of pens had been donated in 2010 and these needed to be used by the end of the transition period, ie 30 April 2011. The Appeal Board noted that whilst Janssen had donated the pens to BRS it was not thereby absolved of all responsibility under the Code in relation to their future use. Although it was concerned at the large number donated for redistribution, it considered that given the number of attendees at conferences, it was, on balance, not unreasonable for Janssen to assume that the pens would be redistributed by the BRS within a reasonable period of time such that their provision would not be affected by changes introduced in the 2011 Code. The Appeal Board ruled that there had been no breach of Clause 18.3. The appeal on this point was successful.

Complaint received

17 June 2013

Case completed

11 September 2013

EX-EMPLOYEE v GEDEON RICHTER

Meeting tweets

An ex-employee complained about two tweets sent by an events company engaged by Gedeon Richter. Gedeon Richter marketed Esmya (ulipristal acetate) for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

The first tweet sent on 9 November 2012 read 'Register for the event "Sharing surgical experience after the use of ulipristal acetate in fibroid patients"', and a second tweet, sent on 22 November read 'Places available at the Nottingham symposium on uterine fibroids'. The complainant referred to these tweets in his/her appeal in Case AUTH/2580/2/13. That case was about whether an invitation published on the events company's website constituted promotion of a prescription only medicine to the public. The Appeal Board rejected the appeal in that case and upheld the Panel's ruling of no breach of the Code; the complainant had not provided any evidence to show that the details of the meeting at issue in that case had been tweeted. The tweets of 9 and 22 November related to different meetings. During its consideration of Case AUTH/2580/2/13, the Appeal Board was concerned that given the two tweets referred to by the complainant and contrary to Gedeon Richter's submission to the Panel, it was clear that details of other meetings, including the name of a medicine and its indication, had been tweeted.

The complainant noted the Appeal Board's concerns in Case AUTH/2580/2/13 and alleged that the tweets of 9 and 22 November promoted a prescription only medicine to the public.

The detailed response from Gedeon Richter is given below.

The Panel noted that it was not entirely clear whether the complainant's allegation was solely based on the wording of the tweets in question or encompassed the relevant invitations and meetings. It was not the Panel's role to infer details of a complainant's allegation. After careful consideration the Panel concluded that the complaint was about whether the tweets *per se* promoted a prescription only medicine to the public.

The Panel noted Gedeon Richter's submission that the 22 November tweet did not mention the name of a medicine or a company and referred only to spaces being available at the Nottingham symposium on uterine fibroids. The Panel did not consider that the tweet advertised a prescription only medicine to the public as alleged. No breach of the Code was ruled.

Conversely, the Panel considered that the tweet of 9 November was promotional because it named a prescription only medicine (ulipristal acetate) and

referred to a potential use (in fibroid patients). The meeting referred to was a Gedeon Richter meeting. The Panel did not consider that Gedeon Richter's submission that the tweet would not have been seen by a wide audience based on the low number of followers the events company had on twitter (55) and the time that the tweet was released (1:37am) was relevant in relation to the requirements of the Code. The Panel noted that the nature of twitter was such that tweets could be broadly and quickly disseminated making them available in the public domain and so in that regard the Panel considered that a prescription only medicine had been advertised to the public. A breach of the Code was ruled.

The Panel noted Gedeon Richter's submission that the tweets were sent by the events company without its knowledge or authority. It was an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf. High standards had not been maintained. A breach of the Code was ruled.

The Panel noted that promoting a prescription only medicine to the public was a serious matter. In addition, the Panel was concerned that Gedeon Richter could not identify a contract or similar material which set out the role and responsibilities of the events company in relation to the materials at issue. The Panel was very concerned that Gedeon Richter had failed to establish a compliance infrastructure for the relationship. The Panel further noted that the lack of any formal agreement between the two parties was only brought to Gedeon Richter's attention by the events company which, following a request from Gedeon Richter in relation to this case for any agreements that were in place between the two, stated that there were no formal documents outlining Gedeon Richter's expectations. The Panel considered that Gedeon Richter had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

An ex-employee of Preglem UK (a wholly owned subsidiary of Gedeon Richter) complained about two tweets sent by an events company engaged by Gedeon Richter. The first tweet, sent on 9 November 2012 read 'Register for the event "Sharing surgical experience after the use of ulipristal acetate in fibroid patients"' and the second tweet, sent on 22 November read 'Places available at the Nottingham symposium on uterine fibroids'. The complainant referred to these tweets in his/her appeal in Case AUTH/2580/2/13. That case was about whether an invitation published on the events company's website constituted promotion of a prescription only medicine to the public. The Appeal Board rejected

the appeal in that case and upheld the Panel's ruling of no breach of the Code; the complainant had not provided any evidence to show that the details of the meeting at issue in that case had been tweeted. The tweets of 9 and 22 November related to different meetings. During its consideration of Case AUTH/2580/2/13, the Appeal Board was concerned that given the two tweets referred to by the complainant and contrary to Gedeon Richter's submission to the Panel, it was clear that details of other meetings, including the name of a medicine and its indication, had been tweeted.

Gedeon Richter marketed Esmya (ulipristal acetate) which was indicated for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

COMPLAINT

The complainant noted the Appeal Board's concerns in Case AUTH/2580/2/13 and alleged that two tweets sent by an events company engaged by Gedeon Richter promoted a prescription only medicine to the public. The first tweet, sent on 9 November 2012 read 'Register for the event "Sharing surgical experience after the use of ulipristal acetate in fibroid patients"' and the second tweet, sent on 22 November read 'Places available at the Nottingham symposium on uterine fibroids'.

When writing to Gedeon Richter, the Authority asked it to respond in relation to Clauses 2, 9.1 and 22.1.

RESPONSE

Gedeon Richter strongly refuted any suggestion that it had intentionally deceived the Panel. The information provided during communications with the Panel, had been open, honest and always what Gedeon Richter believed to be the absolute truth without exception.

The events company had not been as passive as initially thought and unbeknownst to Gedeon Richter and some of the events company employees, tweets in relation to Gedeon Richter meetings had been released.

Gedeon Richter noted that the complaint was about whether tweets released by the events company, engaged by Gedeon Richter, on 9 and 22 November promoted a prescription only medicine to the public. Gedeon Richter first became aware of these tweets when the complainant provided them to the Appeal Board in relation to Case AUTH/2580/2/13.

Gedeon Richter submitted that the tweet released by the events company on 22 November 2012, 'Places available at the Nottingham symposium on uterine fibroids', did not mention the name of a medicine nor the name of a company. It merely referred to a disease area and as such the company denied a breach of Clause 22.1.

Gedeon Richter stated that it was important to consider whether the text of the tweet released on 9 November 2012 'Register for the event "Sharing

surgical experience after the use of ulipristal acetate in fibroid patients"' could be considered promotional in breach of Clause 22.1 as well as the likely audience. The tweet did not mention the clinical benefits or therapeutic indication of ulipristal acetate nor did it mention the brand name or dosage. Gedeon Richter noted that another formulation of ulipristal acetate at a different dosage was an entirely different medicine marketed by another manufacturer for a different indication. Gedeon Richter submitted that given the lack of therapeutic indication or any claim, the tweet did not promote a prescription only medicine to the public and it thus denied a breach of Clause 22.1.

Gedeon Richter further noted that the events company had 55 followers as of 2 July 2013 and its tweets were only visible to the events company's followers or those who actively sought out the events company's twitter feed. The tweet was sent at 1.37am therefore Gedeon Richter considered it was extremely unlikely that it would have been received and read by a wide audience.

Gedeon Richter refuted the allegation that the tweet sent on 9 November was in breach of Clause 22.1 given that the content of the tweet was not overtly promotional, the low number of the events company twitter followers and the early hour at which the tweet was released. Gedeon Richter thus disagreed that it had failed to maintain high standards or had brought discredit upon or reduced confidence in the industry. The company denied breaches of Clauses 9.1 and 2.

Gedeon Richter further noted that its relationship with the events company had evolved over time and lengthy discussions outlining the specific details of each project took place prior to implementation all with the expectation that the support provided by the events company would be passive and in line with the Code.

Gedeon Richter enclosed copies of correspondence with the events company which it submitted confirmed that the events company had not been instructed by Gedeon Richter to release tweets about its events.

In summary, Gedeon Richter had not known about the tweets released by the events company until they had been provided to the Appeal Board by the complainant as evidence in an earlier complaint. The tweets had been removed as soon as Gedeon Richter knew about them and to avoid any further difficulties, no tweets relating to Gedeon Richter events had been issued since.

PANEL RULING

The complaints procedure relied upon complainants providing comprehensive details about their complaint. It was not the Panel's role to infer details of a complainant's allegation. The Panel noted that the scope of the complaint was such that it was not entirely clear whether the allegation was solely based on the wording of the tweets in question or encompassed the relevant invitations and meetings.

The Panel noted that the previous case, Case AUTH/2580/2/13, concerned the invitation.

The Panel considered the matter carefully and decided that as the complaint explicitly referred to the tweets and did not mention the invitations or meetings, it would consider the complaint on that narrow basis. The Panel thus understood the basis of the current complaint to be about the wording of the tweets and whether they promoted a prescription only medicine to the public. The meetings or material linked to the tweets were not considered during the Panel's consideration of this case.

The Panel noted that Clause 22.1 prohibited the advertising of prescription only medicines to the public.

In its guidance on digital communications (updated October 2012) and in relation to twitter, the Authority had stated that 'If a company wanted to promote a medicine via twitter it would have to ensure that if the medicine was prescription only, the audience was restricted to health professionals and that the message, in addition to any link to further information, complied with the Code. In addition companies would also have to ensure that recipients had agreed to receive the information. Given these restrictions and the character limit on twitter, it is highly unlikely that the use of this medium to promote prescription only medicines would meet the requirements of the Code'.

The Panel considered each tweet separately.

- 'Places available at the Nottingham symposium on uterine fibroids'

The Panel noted Gedeon Richter's submission that the 22 November tweet did not mention the name of a medicine or a company and referred only to spaces being available at the Nottingham symposium on uterine fibroids. The Panel did not consider that the content of the tweet constituted advertising a prescription only medicine to the public as alleged. No breach of Clause 22.1 was ruled. Given this ruling no breaches of Clauses 2 and 9.1 were also ruled.

- 'Register for the event "Sharing surgical experience after the use of ulipristal acetate in fibroid patients"'

The Panel disagreed with Gedeon Richter's submission that the content of the 9 November tweet was not overtly promotional. The Panel noted

that the tweet named a prescription only medicine (ulipristal acetate) and referred to a potential use (in fibroid patients) and thus considered that it was promotional. The meeting referred to was a Gedeon Richter meeting. The Panel noted Gedeon Richter's submission that the tweet would not have been seen by a wide audience based on the number of the events company's twitter followers and the time at which it was released but did not consider that this was relevant in relation to the requirements of Clause 22.1. Gedeon Richter submitted that the tweet would only be visible to those who either followed the events company on twitter or sought its twitter feed. However, the Panel noted that the nature of twitter was such that tweets could be broadly and quickly disseminated making them available in the public domain and so in that regard the Panel considered that a prescription only medicine had been advertised to the public. A breach of Clause 22.1 was ruled.

The Panel noted Gedeon Richter's submission that the tweets were sent by the events company without its knowledge or authority. It was an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf. High standards had not been maintained. A breach of Clauses 9.1 was ruled.

The Panel noted that promoting a prescription only medicine to the public, contrary to Clause 22.1, was a serious matter. In addition, the Panel was concerned that Gedeon Richter could not identify a contract or other material which clearly set out the role and responsibilities of the events company in relation to the materials at issue. Whilst the Panel accepted that Gedeon Richter had, to a degree, been let down by the third party, it was very concerned that Gedeon Richter had failed to establish a compliance infrastructure for the relationship. The Panel further noted that the lack of any formal agreement between the two parties was only brought to Gedeon Richter's attention by the events company which, following a request from Gideon Richter in relation to this case for any agreements that were in place between the two, stated that there were no formal documents outlining Gedeon Richter's expectations. The Panel considered that Gedeon Richter had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received

18 June 2013

Case completed

5 August 2013

PSYCHIATRIST v AMDIPHARM MERCURY

Alleged unsolicited email

A child and adolescent psychiatrist, complained about an unsolicited, promotional email for Nipatra (sildenafil) sent on behalf of Amdipharm Mercury. Nipatra was indicated for the treatment of men with erectile dysfunction.

The detailed response from Amdipharm Mercury is given below.

The Panel noted that the complainant had received the email via his NHS email account. The Panel further noted that Amdipharm Mercury via a third party had a contract with the database provider for Nipatra email campaigns and that the database provider had obtained consent from the complainant when he completed his registration. An email to the complainant in April 2010 described the registration process for another service and explained that from time to time, 'pharmaceutical promotional materials' would be sent by email. The unsubscribe facility which stated 'If you do not wish to receive such information please click the box*' appeared at the very end of the email after the signature and contact details. It was clear that the company intended to email promotional material from pharmaceutical companies. The Panel noted that the complainant was emailed in June and November 2012 to confirm his registration and give him the opportunity to opt-out of receiving information as detailed above. It was not clear that the complainant had opted-in or out following the emails of June and November 2012. Amdipharm Mercury had submitted that recipients stayed on the database if they could not be reached or if they did not click the opt-out link.

Nonetheless, the Panel considered that by registering on the site and failing to subsequently unsubscribe, the complainant had given prior permission to receive, *inter alia*, promotional material by email and no breach of the Code was ruled.

The Panel noted Amdipharm Mercury's submission that the complainant could have opted-out of receiving further promotional emails by using the opt-out link or by directly contacting the database on the telephone number provided, both of which were included at the bottom of the email at issue. The Panel noted that the complainant had tried to unsubscribe to the email by replying to it rather than using the recommended opt-out link provided and had not tried to telephone the database direct. In this regard, the Panel ruled no breach of the Code.

The Panel did not consider that Amdipharm Mercury had failed to maintain a high standard and no breach of the Code was ruled. The Panel noted its rulings above and ruled no breach of Clause 2.

During the consideration of this case the Panel queried why the complainant, a child and adolescent

psychiatrist, was emailed about a product indicated for the treatment of erectile dysfunction.

A child and adolescent psychiatrist, complained about an email (ref UK/NIP/NHS/428D/2013) for Nipatra (sildenafil) sent on behalf of Amdipharm Mercury Company Limited. Nipatra was indicated for the treatment of men with erectile dysfunction.

COMPLAINT

The complainant provided a copy of the email at issue and stated that his subsequent email to 'EDtreatments@datafor NHS.com' was apparently undeliverable. This subsequent email read:

'I am very unhappy that despite trying to unsubscribe to emails like this I keep on receiving them.

I would like to know where you got my email address from and what other information is held on the database from which it came and how my details were given to that database. I would like all my details to be removed from that database.'

When writing to Amdipharm Mercury, the Authority asked it to respond to Clauses 2, 9.1 and 9.9 of the Code.

RESPONSE

Amdipharm Mercury explained that it engaged a digital media buying company which was part of a larger digital media agency which had been in existence since 2002 and specialised in, *inter alia*, online advertisements. Amdipharm Mercury had worked with this digital media agency for the last four years to perform its digital media buying. The agency had booked digital campaigns for Amdipharm Mercury with a number of channels. The agency also commissioned email slots with a third party database which was a database of UK medical professionals employed within the NHS and private healthcare sectors. Amdipharm Mercury stated that the complainant was registered as a member on the third party database and it was through this database that he was sent the email at issue. On receipt of the complaint Amdipharm Mercury held discussions with the large digital media agency and the third party database provider in order to help it fully investigate all necessary aspects around the complaint.

Amdipharm Mercury provided a copy of a document which set out the step-by-step procedure for engaging customers and registering them with the database.

An operative employed by the database provider would initially telephone the doctor and then a

registration email was sent to the doctor to confirm the telephone conversation and invite him/her to complete the online registration using the access code provided. A copy of the email, dated 16 April 2010, sent to the complainant with his access code was provided. The registration email stated that the database provider would from time to time send information by e-mail about its associated/affiliated companies and their clients' product and services, which might include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information. At the end of the email an opt-out tick box was provided for those who did not wish to receive the information. The complainant was given this opportunity to opt-out when he registered but he did not do so.

The complainant successfully registered as a member of the database in May 2010, a copy of the registration confirmation email was provided.

Health professionals could only complete the registration once they had accepted the terms and conditions of the database website which might then allow information about affiliated organisations including promotional emails to be sent to them.

A screen shot of the registration form for the database was provided. The information gathered at the time of registration included; the health professional's name, organisation and address, telephone number, email address and a description of duties and areas of medical interest. This was the only page which was issued to collect information. A copy of the complainant's completed form was provided. The company stated that this information could be shared with the complainant in response to his desire to know what information was held about him.

Amdipharm Mercury explained that health professionals could leave the database at any point if they contacted the database provider either by using the opt-out option provided or telephoning a given number.

All emails sent to the health professional offered the option to opt-out of receiving further emails. The complainant had had this option open to him on several occasions but had not used it. It was estimated that the database provider had sent the complainant approximately 30-40 emails since he first registered in 2010.

When health professionals clicked the opt-out link, they were taken to an automated webpage which stated that they had been opted out. A copy of the screen grab was provided. The health professional was removed from receiving all emails immediately and indefinitely and his/her name was recorded in an unsubscribed folder in the database. The unsubscribed email folder was used by the database provider before each transmission, to double check that no unsubscribed health professional received any further emails.

Amdipharm Mercury noted that the complainant had stated that he had tried to unsubscribe several

times to 'emails like this' but he continued to receive them. There was no evidence to suggest that the complainant tried to opt-out of receiving emails from the database provider. Amdipharm Mercury noted that the complaint was general and did not specifically apply to emails sent by the database provider in question.

Amdipharm Mercury also noted that when the complainant tried to contact the database provider, his reply to the email address was undeliverable. This was not the recommended pathway for anyone looking to unsubscribe from the database provider's emails. Had the complainant followed the instructions to opt-out, he would not have encountered this problem as his email would have been received. The agency confirmed that the opt-out email always worked and was checked for functionality before emails were sent; checking that the opt-out link worked was a fundamental part of the test-run process, and nothing was sent without one. Additionally, the link did not have a time limit nor did it expire at any stage.

The database provider went even further and provided a contact telephone number for anyone who wished to unsubscribe in case they wanted to speak to someone directly.

Each doctor was called annually. If the doctor could not be reached the name would stay on the database list. Recipients would stay on the database list unless they clicked the opt-out option. A copy of the emails sent to the complainant in June as well as November 2012 were provided, the opt-out box was not clicked and so he remained on the database.

Amdipharm Mercury provided an email from an employee of the database provider who had spoken to the complainant in the course of investigating his complaint. The complainant acknowledged that he had not used the unsubscribe button at all, which he agreed was the correct method, but instead had attempted to return the agency email. It was unfortunate that at the time, the agency had experienced a brief outage and therefore the email could not be delivered. The complainant also stated that his general comments about being unable to opt-out previously referred to other emails which he had received from other sources.

The information presented above outlined that the agency took several steps to ensure that health professionals registered to the database in an informed and rational manner. All necessary documentation specific to the complainant's engagement and registrations had been provided. Amdipharm Mercury submitted that its agency adopted high standards at all times and that there had been no breach of Clauses 9.1 and 2. The complainant gave his consent and permission to receive email information from time to time which could have included promotional information. Each email sent to the complainant included information on how he could opt-out if he so wished. In this case, more than one option was available (email and telephone). The company denied a breach of Clause 9.9.

In conclusion, Amdipharm Mercury submitted that it (and the agencies acting on its behalf in this case) had maintained high standards in procedure, content and documentation and had therefore not breached the Code.

PANEL RULING

The Panel noted that the complainant had received via his NHS email account a promotional email for Nipatra. The Panel noted that Clause 9.9 prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel noted that Amdipharm Mercury via a third party had a contract with the database provider for Nipatra email campaigns.

The Panel noted Amdipharm Mercury's submission that the complainant was registered as a member on the database and the database provider had obtained consent from the complainant when he completed his registration. An email to the complainant in April 2010 described the registration process for another service and explained that it '... will from time to time send information by e-mail about our associated/affiliated companies and their clients' product and services, which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information'. This was followed by a new paragraph 'However, please be advised that we will not share your e-mails with any third parties'. The unsubscribe facility which stated 'If you do not wish to receive such information please click the box*' appeared at the very end of the email after the signature and contact details. It was clear that the company intended to email promotional material from pharmaceutical companies. The Panel noted that the complainant was emailed in June and November 2012 to confirm his registration on the database and give him the opportunity to opt-out of receiving information as detailed above. Information provided by the agency stated that when health professionals were contacted annually to confirm their contact details, once the information had been confirmed they would be sent the opt-in statement. To proceed recipients had to acknowledge the opt-in statement. It was not clear that the complainant had opted-in or out following the emails of June and November 2012. Amdipharm Mercury had submitted that recipients

stayed on the database if they could not be reached or if they did not click the opt-out link.

Nonetheless, the Panel considered that by registering on the site and failing to subsequently unsubscribe, the complainant had given prior permission to receive, *inter alia*, promotional material by email. No breach of Clause 9.9 was ruled.

The Panel noted that the supplementary information to Clause 9.9 required that where prior permission to use emails for promotional purposes had been granted each email should have an unsubscribe facility. The Panel noted Amdipharm Mercury's submission that the complainant could have opted-out of receiving further promotional emails by using the opt-out link or by directly contacting the database on the telephone number provided, both of which were included at the bottom of the email at issue. The Panel noted that the complainant had tried to unsubscribe to the email by replying to it rather than using the recommended opt-out link provided and had not tried to telephone the database direct. In this regard, the Panel ruled no breach of Clause 9.9.

The Panel did not consider that Amdipharm Mercury had failed to maintain a high standard. No breach of Clause 9.1 was ruled. The Panel noted its rulings above and ruled no breach of Clause 2.

During the consideration of this case the Panel noted that Clause 11.1 of the Code required that promotional material should only be sent to those whose need or interest in the particular information could be reasonably assumed. In that regard, the Panel queried why the complainant, a child and adolescent psychiatrist, was emailed about a product indicated for the treatment of erectile dysfunction. The Panel noted that the database provider informed Amdipharm Mercury that in his role as the lead consultant, the complainant had to be consulted prior to all purchases and was therefore listed as a payor within the database. The Panel queried, however, whether the complainant would be consulted on purchases outside of his specialist area.

Complaint received	18 July 2013
Case completed	29 August 2013

VOLUNTARY ADMISSION BY NAPP

Promotional emails sent without recipient's permission

Napp voluntarily reported three incidents which related to a call process conducted by a contract tele/e-detail sales agency, on its behalf. The incidents related to BuTrans (buprenorphine patch) promotional emails sent to two practice managers and one health professional. Napp was uncertain as to whether the recipients had given their consent to receive such emails.

In accordance with Paragraph 5.6 of the Constitution and Procedure for the PMCPA, the Director treated the matter as a complaint.

Napp explained that the agency would schedule an appointment with a customer for a later web-based e-detail call by an agency sales representative. This offered health professionals unable to see a representative, the opportunity to learn more about a medicine via a real-time, web-based interface or by telephone. The call scheduling process involved a scripted call usually with a receptionist, an email to confirm the appointment and another to explain the format if there were any questions. The confirmation email had two sections; the first explained that a conversation had taken place to book the appointment and the second was addressed to the health professional to confirm the appointment details. The emails were only sent if an email address was supplied by the receptionist or similar who made the appointment.

The agency used health professional data provided by Napp to populate certain data fields within the call system including name, address, institution and telephone numbers. Napp noted that there was no email data field within the call system.

At the end of a scheduled web-based e-detail or telephone call, the health professional could agree to receive or specifically request that additional BuTrans promotional material be posted or emailed.

Napp approved a template letter/email to be used by its employees to send out any additional BuTrans information requested following a call. Confirmation emails from schedulers and follow-up additional information emails from Napp were only sent if an email address was supplied to the agency by a health professional.

Napp submitted that the three incidents which took place in May and June 2013, involving the same agency sales representative, involved uncertainty around the consent given for three health professionals to receive emails containing additional promotional information following a call. Napp immediately launched an investigation and services were suspended.

In the first incident Napp understood that the representative initially called a doctor in early May

2013 but was advised that he did not speak to representatives and was asked to call back to speak to the practice manager which the representative did a few days later. The relevant call notes recorded, *inter alia*, that the practice manager had requested additional BuTrans information. It was, however, not clear from the notes whether this had been specifically requested to be sent by email. (Napp noted that the representative's call notes for the three incidents lacked detail). Napp used its template email and sent two pieces of material to the practice manager, both attachments required the recipient to click on them to open them and the email explained that the attachments were promotional and advised the reader not to open them if they did not wish to see them. The practice manager subsequently contacted Napp and stated that she had not requested any information from the representative. Napp apologised for any unexpected communication. No further communication had taken place.

In the second incident Napp understood that the representative similarly called a doctor who did not speak to representatives and was again asked to call the practice manager. The representative called the practice manager. Once again, the representative's notes recording the call with the practice manager suggested that additional BuTrans information had been requested but it was not clear whether this was specifically requested to be sent by email. Napp emailed BuTrans documents to the practice manager who emailed straight back explaining that she had not had the conversation referred to in the email (an 'online conversation') and wondered if Napp had sent it to the right person.

Napp understood that the representative stated that he/she had gained express permission from the practice manager. Napp directed the project manager to send his/her team an email on the Code requirements and guidance on obtaining email consent and the customer was removed from further calling on the project.

Napp apologised to the practice manager for the delay in responding as well as for any error which might have occurred. No further communication had taken place.

In the third incident Napp understood that the representative initially called a doctor but was advised to call back the following week. A call back was made but the representative was redirected to the practice manager as the doctor was unavailable. The call notes suggested that the practice manager had thought the doctor's partners would be interested in the product information and requested that it be sent to another named doctor.

In this instance, the notes specifically referenced to the information being emailed. Napp emailed BuTrans information to the second named doctor as requested by the representative.

The second named doctor responded and explained that he had not had an online conversation and did not wish to receive any information. Napp apologised and its investigation into the matter had shown it likely that no consent was given by the doctor for the use of email in this way. Napp submitted, however, that the practice manager operated under implied authority to give such permission on behalf of colleagues. In this instance it was likely that the representative obtained the doctor's email address from the practice manager.

The detailed response from Napp is given below.

The Panel noted that Napp's investigation into the three incidents had been hampered by the representative's persistent poor record keeping.

The Panel noted that the Code stated that email communications must not be used for promotional purposes, except with the prior permission of the recipient. In the Panel's view this permission had to be obtained from the recipient of the material and could not be given by a third party on the recipient's behalf. In that regard the Panel noted that an email in late May from one of the agency's sales managers to his/her sales team clearly stated that email addresses of health professionals given by receptionists and support staff could not be used without direct permission from the recipient.

The Panel considered each incident separately.

1 Practice Manager

The Panel noted that on receipt of emailed, additional BuTrans information, the practice manager had emailed Napp to inform the company that she had not requested any information, that she did not want to receive any further information and that her email address should be removed from its circulation list. The practice manager referred to the representative by name but did not state whether she had given him her email address. The representative's call notes stated that 'the customer requested med info' but did not state how such information was to be sent. Napp did not know how the representative had obtained the practice manager's email address. The Panel noted that extreme dissatisfaction was generally required before an individual was moved to complain but considered that on the basis of the information before it, it was impossible to know whether the practice manager had given her email address, and her permission to use it for promotional purposes, to the representative. The Panel therefore ruled no breaches of the Code.

2 Practice Manager

The Panel noted that Napp had emailed the practice manager with additional BuTrans information and that in response the practice manager had stated that she had not had the conversation referred to in

the email and queried whether Napp had sent the information to the right person. The Panel noted that Napp's email template referred to a 'recent online conversation' and Napp's submission that the representative had telephoned the practice manager and that this might explain why she could not remember the conversation. The Panel noted Napp's submission that the representative's call logs showed that three calls had been made to the practice in question and although the call notes were not detailed, they stated that information had been requested. The call notes did not state how the information was to be sent but the Panel noted that Napp understood that the representative had stated that he had gained express permission from the practice manager given the previous incident and further instructions from Napp. The Panel further noted Napp's submission that email addresses were not stored in the call system and the original appointment had been made with a different health professional so it was difficult to rule out the possibility that the email address had been obtained during a telephone conversation. As above, the Panel considered that it was impossible to know whether the practice manager had spoken to the representative and given her email address, and her permission to use it for promotional purposes. The Panel therefore ruled no breaches of the Code.

3 Practice Manager and Doctor

The Panel noted that following receipt of an email about BuTrans, a doctor emailed Napp stating that he had not had an online conversation with the representative as stated in the email and did not wish to receive any information. In subsequent correspondence, the doctor queried how his contact details had been obtained as he had not shared them. The Panel noted Napp's submission that the practice manager had provided the representative with the doctor's email address and instructed him to send the additional BuTrans material. This was supported by the representative's brief call notes. The Panel noted, however, that in a further email to Napp, the doctor stated that the practice manager had no recollection of any conversation with the representative at issue and that he would not have revealed the doctor's email address in conversation with a representative. The Panel noted Napp's submission that as the doctor used a short form of his name in his email address the representative was unlikely to have been able to guess it and so he must have been given it by someone; it appeared clear, however that that someone was not the doctor. The Panel considered that the doctor had been emailed promotional material without his prior permission and that the representative had not maintained a high standard of ethical conduct. Breaches of the Code were ruled.

Napp Pharmaceuticals voluntarily reported three incidents which related to a call process conducted by a contract tele/e-detail sales agency, on its behalf. The incidents related to BuTrans (buprenorphine patch) promotional emails sent to two named practice managers and one named health professional. Napp was uncertain as to whether the recipients had given their consent to receive

such emails. Following an investigation, Napp was not certain that the incidents at issue breached the Code but submitted that combined, they should be reported to the Authority.

In accordance with Paragraph 5.6 of the Constitution and Procedure for the PMCPA, the Director treated the matter as a complaint.

VOLUNTARY ADMISSION

Napp explained that the call system involved an agency 'scheduler' scheduling an appointment with a customer for a later web-based e-detail call by an agency sales representative. This method of communication offered health professionals unable to commit to physically seeing a representative, the opportunity to learn more about a specific medicine via a real-time, web-based interface or by telephone. Napp understood that this method of communication was becoming more common within the industry and the agency provided similar services to other pharmaceutical companies.

The call scheduling process involved a scripted call usually with a receptionist, an email to confirm the appointment and another to explain the format if there were any questions. The confirmation email had two sections; the first section explained that a conversation had taken place to book the appointment and the second was addressed to the health professional to confirm the appointment details. The two emails were only sent if an email address was supplied by the likes of the receptionist who made the appointment.

The agency in question used health professional data provided by its clients and had in this instance used data from Napp to populate certain data fields within the call system including name, address, institution and telephone numbers. Napp noted that there was no provision of email data fields within the call system.

At the end of a scheduled web-based e-detail or telephone call, the health professional could agree to receive or specifically request additional BuTrans promotional material to be posted or emailed to them.

Napp had commissioned the agency to conduct promotional tele/e-detail BuTrans sales calls to health professionals in October 2012; a considerable amount of due diligence was undertaken during the negotiation of the contract, in respect of the call system and the agency's process surrounding it. Napp submitted that it had taken steps to fully understand the system and how health professionals would interact with it and agency employees, and had imposed extensive contractual obligations upon the agency in relation to the general performance of the project and quality of the services provided by it and its employees.

The agency was required to:

- use all reasonable skill and care in the performance of these services. This clause was particularly important to Napp within its contracts

and Napp sought to monitor and enforce it diligently

- accept extensive contractual obligations imposed on it by Napp in respect of recruitment and disciplinary matters in relation to staff working on the project
- provide a scheduling and sales representative team dedicated to Napp for the duration of the contract
- comply with all reasonable instructions from Napp which included compliance with appropriate elements of its standard operating procedures (SOPs) relevant to the detailing and promotion of medicines
- comply with all relevant laws, regulations and policies, including the Code, relevant to the detailing and promotion of medicines
- ensure that it 'used best endeavours under all circumstances' to respect and adhere to Napp's Leadership Attributes and Code of Business Ethics (both of which were appended to the contract)
- ensure and maintain evidence that its sales staff were ABPI qualified (the certificate of qualification for the relevant representative was provided)
- provide a project manager pursuant to the contract to undertake the general management of its employees as well as the specific management tasks imposed upon she/he by the contract.

Napp submitted that fees and incentives for agency staff were set at the appropriate levels to avoid them being an undue proportion of their basic salary and to avoid excessive call rate activity.

Before the project started, Napp reviewed and approved all of the associated materials and scripts that would be used by agency employees. Napp took additional steps to guide the agency where it believed particular Code areas required it and in this regard had focussed on the emailing of promotional materials to health professionals. In particular:

- data protection obligations were placed on the agency
- the agency was contractually required to focus on a target list of circa 13,000 health professionals provided to it by Napp from its validated database. Annual call rates were set within the contract at appropriate Code compliant levels to avoid excess call rate activity
- key performance indicators were included in the contract to enable Napp to monitor and measure the agency's performance in terms of call targeting, in-call activity and call quality
- the agency was required to provide Napp with a monthly record of all calls
- the contract with the agency required its employees to undergo training with Napp in respect of the project. Napp trained agency employees on its anti-corruption policy requirements as well as additional ABPI training including specific guidance on the use of health professionals' email addresses
- the agency was obliged to only use materials provided (and approved) by Napp, including anything requested by a health professional to be sent by post or email

- it was agreed with the agency that, as an additional control for Napp, any additional information requested by a health professional following a call would be sent by a Napp employee using a Napp email address. This particular step was included to limit email activity by agency staff to schedule confirmations and call information. This helped Napp ensure that only approved materials and information were sent to the right people. It was recognised that this was always subject to a certain level of reliance upon agency employees communicating accurate email addresses and consents to Napp. Napp submitted that the Code did not require formal written consent regarding email use and was guided by the expertise and pharmaceutical industry experience of the agency in respect of this project together with the other safeguards that it employed

In addition to the above, Napp submitted that it had approved a template letter/email which would always be used by its employees to send out any additional BuTrans information requested following a call. This template was set out below:

'Dear []

Further to your recent online conversation, [representative name], your NappCall representative has indicated to me that you have requested some supporting information about the BuTrans patches that were discussed. The items requested are marked below:

- BuTrans monograph (PDF attached to this email)
- FAQ booklet 'Your questions answered' (Enclosed)
- Patients in specific populations (PDF attached to this email)
- Patient booklet 'Your guide to BuTrans patches' (Enclosed)

Please note that if you have requested items that are attached as PDFs to this email, these items contain promotional information. If you do not wish to see this information please refrain from opening the PDF(s) attached.

Any items to be sent by post should reach you in the next few days.

If you have any further questions please do not hesitate to contact me.'

Napp stated that it had specifically structured this template email so that health professionals did not see the requested promotional information in the main body of the email. Napp recognised the potential for the agency's experience with industry practice in obtaining email permission to inadvertently expose health professionals to material that they might not remember asking for. Napp wanted to give health professionals a further opportunity to decide if they wanted to view promotional content or not. Napp reiterated the importance of adherence to the Code in an email sent in January 2013 to the agency and its respective

sales representatives which included a specific attachment where Clause 9.9 was definitively reiterated and emphasised. Napp noted that within the call system, there was no field for the inclusion of health professionals' email addresses (regardless of whether these were available from the likes of named data providers Napp or agency databases). The fields were limited to name, address, institution and telephone numbers. The stance taken by the agency was as follows: 'At the start of the project we agree use of email with our client and this is minimised to avoid email usage unless absolutely necessary within the constraints of the Code. This guidance is communicated to call representatives both verbally and in writing. In addition to this our customer data does not include email addresses and therefore emails could only be sent if an email address is provided to us'.

Consequently, confirmation emails from schedulers and follow-up additional information emails from Napp were only sent if an email address was supplied to the agency by a health professional.

Napp submitted that between November 2012 and June 2013, the agency recorded over 2,100 calls on health professionals on behalf of Napp. The three incidents leading to this voluntary admission took place in May and June 2013. Each incident involved calls to health professionals by the same agency sales representative following appointments booked by agency schedulers. The key aspect of all three incidents, and the purpose of Napp's voluntary admission, related to uncertainty around the consent given for three health professionals to receive emails containing additional promotional information following a call.

Napp apologised to each of the health professionals, including two practice managers and one GP, for any misunderstanding. No further correspondence had been received since the last communication in June 2013. Napp submitted that this was an isolated and contained episode and no further notifications had been received from any other health professionals called upon by the agency.

Upon becoming aware of the incident, Napp immediately launched an investigation and further services performed by the agency were initially suspended pending its outcome as additional information was obtained from the agency and the call servers based in another European country. The contract with the agency was terminated by Napp in July 2013 following the disclosure and interpretation of further information. In addition, the investigation led to the agency's dismissal of the representative involved in these incidents and disciplinary action pending against the relevant project manager responsible for the representative.

Napp detailed three incidents.

1 Practice Manager

Napp understood that the representative initially called a doctor in early May 2013 but was advised that he did not speak to representatives and was

asked to call back to speak to the practice manager. A call back was made when the representative spoke to the practice manager.

Napp understood that a brief discussion took place about Napp's product and the practice manager had requested additional BuTrans information. This was suggested in the sales manager's call notes. It was, however, not clear from the notes whether this had been specifically requested to be sent by email. The reference simply to 'med info' being requested was not ideal although this phrase was used on all of the representative's notes. Napp generally only made four pieces of additional information available and the representative had specified in instructions to Napp which material had been requested. Napp noted that during its investigation, it had found that the particular representative's call notes for the three incidents at issue lacked detail.

Napp used its template email and sent two of the possible four pieces of material to the practice manager. Both attachments required the recipient to click on them to open them and read them and the email explained that the attachments were promotional and advised the reader not to open them if they did not wish to see them.

The practice manager subsequently contacted Napp and stated that she had not requested any information from the representative. Napp apologised for any unexpected communication. No further communication had taken place between the parties since.

Despite Napp's investigation it was not possible to definitively conclude either way as to whether any consent was given by the practice manager for the use of her email in this way. The call notes were not ideal yet they stated that information was requested. Napp submitted that email addresses were not stored in the call system. Napp had looked into whether the representative had obtained the email address from the scheduler's notes yet the scheduler had made an appointment with someone else. Napp had also considered the possibility that the representative had guessed the email address, however in this instance the practice manager used a different email address from the name on her email signature and the name she went by on the surgery website. Notwithstanding the practice manager's denial, Napp concluded that it was difficult to rule out the possibility that an email address had been provided for this additional information to be sent.

Following this incident coming to Napp's attention, it called the project manager at the agency to communicate the issue. It was agreed that the project manager would speak to the representative in question to reinforce the Code requirements and Napp's direction about the use of email. This action was communicated back to Napp and, as per the practice manager's requirements, she was removed from further calling on the project.

As the telephone number to the practice manager was a local number, it had not been possible to itemise the particular call to investigate its duration

or any other circumstantial evidence which might be gleaned from it.

2 Practice Manager – 16 May 2013

Napp's investigation into this incident suggested that it followed a similar pattern to that above. Napp understood that the representative initially called a doctor in May 2013 and was advised that the doctor did not speak to representatives and was asked to call back to speak to the practice manager. A call back was made when the representative spoke with the practice manager.

Napp understood that a brief discussion took place about Napp's product and additional BuTrans information had been requested by the practice manager. Once again, this was suggested in the representative's call notes but it was not clear from the notes whether this was specifically requested to be sent by email.

Napp used its email template to send two of the possible four pieces of material to the practice manager, namely a BuTrans monograph, and a 'Patients in Specific Populations' booklet. The recipient had to click on both attachments in order to open and read them and the email explained that the attachments were promotional and advised the reader not to open them if they did not wish to see them.

On the same day, the practice manager emailed Napp explaining that she had not had the conversation referred to in the email (an 'online conversation') and wondered if Napp had sent it to the right person.

When this incident came to Napp's attention, it was communicated to the agency's project manager by telephone. It was agreed that the project manager would once again speak to the representative. Napp understood that the representative stated that he had gained express permission from the practice manager in light of the previous incident and the reiteration of direction from Napp. In addition, the project manager was to send further written communication to his team and an email was circulated in late May to highlight the relevant Code requirements and provide additional guidance on obtaining email consent.

This action was communicated back to Napp and the agency's head of commercial, and the customer was removed from further calling on the project.

Napp apologised to the practice manager for the delay in responding as well as for any error which might have occurred. No further communications had taken place between the parties.

Despite Napp's investigation, it had not been possible to definitively conclude either way as to whether specific consent had been given by the practice manager for the use of her email in this way. The call notes were not ideal yet had stated that information was requested. Once again, Napp noted that email addresses were not stored in the

call system. Napp had looked into whether the representative obtained the email address from the scheduler's notes yet the scheduler again had made an appointment with a different health professional with the representative being redirected to the practice manager. Napp had also considered whether the representative had guessed the email address. Although Napp could not rule this out, it considered it highly unlikely given that such a pattern was not seen across all three incidents.

Given the practice manager's particular response 'I did not have this conversation', Napp had investigated whether the call actually took place. Upon review of the representative's telephone logs, Napp confirmed that three telephone calls were made to the practice in question by the specific representative. The combined duration of these calls was sufficiently long for the recipient to consent to giving her email address out for further information. Napp noted that its email template referred to a 'recent online conversation' which in this situation had been replaced by a telephone call; this could explain why the practice manager could not remember the conversation.

Napp concluded that it was difficult to rule out the possibility that an email address had been provided for the additional information to be sent.

3 Practice Manager and Doctor

Napp submitted that this incident had similarities with the two above with regards to the uncertainty surrounding the use of email although in this case the email was sent directly to a doctor rather than to a practice manager. Napp understood that the representative initially called a doctor in late May 2013 but was advised to call back the following week. A call back was made but the representative was redirected to the practice manager as the doctor was unavailable.

Napp understood that a brief discussion took place about Napp's product and the call notes suggested that the practice manager had thought the doctor's partners would be interested in the product information and requested that it be sent to a second named doctor.

Again, the representative's call notes suggested that the practice manager had requested additional BuTrans information. In this instance, the notes specifically referenced to it being emailed.

Napp received an email request from the representative for the additional BuTrans information to be emailed to the second doctor.

Using the email template, Napp sent the second doctor an email which had PDF files attached containing a BuTrans monograph, and a 'Patients in Specific Populations' booklet. Both attachments required the recipient to click on them before being opened and read. The email explained that the attachments were promotional and advised the reader not to open them if they did not wish to see them.

The second doctor responded and explained that he had not had an online conversation and did not wish to receive any information. Following Napp's apology, the second doctor wished to understand where his contact details had been obtained from. Napp explained that it was in the process of investigating the matter and would provide him with further information once the work had been completed.

Once the initial investigation had been completed, Napp tried unsuccessfully on several occasions to telephone the second doctor following which contact was made and conversation carried out via email to explain the findings of Napp's initial investigation. Since then there had been no further correspondence between the parties.

Napp stated that its investigation had shown it likely that no consent was given by the second doctor for the use of email in this way. Napp submitted that had it known this, it categorically would not have sent him an email with promotional material attached. Napp submitted that it had not been given this crucial information by the representative. Napp further submitted, however, that the practice manager operated under implied authority to give such permission on behalf of colleagues. Napp submitted that the call notes were not ideal yet they did state that information had been requested and importantly that it would be of interest to the second doctor rather than the first doctor with whom the original call had been planned. Napp again noted that email addresses were not stored in the call system and that in this instance it was likely to be obtained from the practice manager despite the confusion about an online conversation taking place with the representative. Napp had looked in to whether the representative had obtained the email address from the scheduler's notes yet the scheduler had again made the appointment with a different health professional, the first doctor, and the representative was redirected to the practice manager who had asked him to email the second doctor. Although Napp could not rule out, the possibility that the representative had guessed the email address, it considered it highly unlikely because such a pattern was not seen across the three incidents and the doctor used a shorter version of his name in his email address.

Napp concluded that it was difficult to rule out the possibility that an email address had been provided by the practice manager for the additional information to be sent to the second doctor; the circumstantial evidence suggested that the practice manager had exercised implied authority to give permission on the second doctor's behalf regarding the use of his email in this way.

When this incident came to Napp's attention, it telephoned the agency's head of commercial and given the two previous incidents, the agency's head of operations contacted the representative to understand the situation.

In conclusion, Napp submitted that a conference call had taken place on 6 June between the agency,

Napp and the senior brand manager. As the agency and its employees had violated the high standards and stringent procedures to abide strictly by the Code, Code of Business Ethics and Leadership Attributes demanded by Napp, Napp requested that the agency launch its own internal investigation into the matter. It was agreed that a disciplinary process be instigated together with the immediate suspension of the representative in question. Napp understood that the disciplinary action ended in the representative's termination given that Napp would have, in any event, exercised its contractual right to request that the representative in question be removed from the particular project.

Napp had requested investigation reports from the agency in order to continue its investigation. At this time Napp formally suspended the contract with the agency with immediate effect, pending a final decision on termination of the contract.

The contract with the agency was terminated in July 2013.

When writing to Napp, the Authority asked it to respond in relation to Clauses 9.1, 9.9 and 15.2 of the Code.

RESPONSE

Napp submitted that since it made its voluntary admission, it had been able to interrogate and gather further information from the agency. In view of the evidence available to Napp at this time as set out above, Napp considered that the incidents in the self-report did not represent breaches of the Code. That said, Napp acknowledged the potential for uncertainty from conflicting information from the respective health professionals should that be available to the PMCPA.

As detailed above, Napp had, through contractual obligations and training, imposed upon the agency and its employees an extensive framework of Codes, policies and procedures to ensure that high standards would be maintained at all times. Therefore, Napp considered that high standards had been maintained. Napp submitted that it had in place appropriate core compliance modules in addition to which Napp and the agency imposed additional bespoke requirements on the agency employees in respect of this project. Therefore Napp submitted that there had been no breach of Clause 9.1.

Napp submitted that Clause 9.9 did not stipulate that written permission must be obtained. Consequently, the use of verbal permission did not constitute non-compliance with this clause. The issue that this clause presented, regarding verbal permission, was one of evidence that such permission was given. It was in that respect Napp believed there to be considerable circumstantial evidence to support no breach of this clause.

The circumstantial evidence indicated that in all three instances permission was obtained. In two of those instances the permission was obtained

directly from the recipients. In the third instance, Napp considered that permission was granted on behalf of the recipient in circumstances where it was reasonable to believe that it was pursuant to the protocols of the practice involved.

There was considerable circumstantial evidence to support the fact that verbal permission had been given by two recipients. The call notes stated that information was requested. As stated in Napp's original letter, email addresses were not stored in the call system which required them to be obtained from a recipient by the agency representatives before such contact could be made. Napp had investigated whether the representative obtained the email addresses from the scheduler's notes yet in each instance, the scheduler had made the original appointment with a different health professional before it was intercepted by the practice manager. Napp had also considered the possibility of the representative guessing the email addresses. There was no evidence of any such pattern existing across the three incidents and in the second incident the practice manager used a different email address from the name on her email signature and the name she went by on the surgery website.

There was also considerable circumstantial evidence in the third incident that permission had been obtained from the practice manager who had operated under implied authority to give such permission on behalf of colleagues. This was reasonable to believe given the evolution of the practice manager's role to help manage what was and what was not sent to or put in front of his/her colleagues. Napp further submitted that Clause 9.9 did not require such permission to be provided directly from the recipient. The call notes stated that information was requested and importantly that such information would be of interest to the second doctor (rather than the first doctor with whom the original call had been planned). Once again, Napp noted that email addresses were not stored in the system and in this instance it was likely to have been obtained from the practice manager (despite any confusion, possibly via the Napp template email, about an 'online conversation' which took place with the representative). Napp had investigated whether the representative had obtained the email address from the scheduler's notes yet the scheduler had again made an appointment with a different health professional the first doctor; the representative was redirected to the practice manager and had seemingly been asked to email a further health professional, the second doctor. Napp had also considered the possibility of the representative guessing the email address. Napp submitted that this was unlikely because such a pattern had not been seen across the three incidents and the doctor referred to a shortened form of his name in his email address.

Napp submitted that in all three instances the evidence supported the fact that verbal permission was obtained. In one instance the permission had been given on behalf of a colleague. Given the evidence available to Napp it refuted that any of the circumstances were in breach of Clause 9.9.

Napp addressed Clause 15.2 below under its two distinct sections. The first was whether the agency representative maintained high standards of ethical conduct in the discharge of his duties. The second was whether he had complied with all of the relevant requirements of the Code.

The extensive framework of Codes, policies and procedures (including its Code of Business Ethics) imposed upon the agency and its employees by Napp was set out above. The agency also imposed its own policies and procedures (including restrictions on access to health professionals' email addresses) as additional safeguards for its employees when interacting with health professionals. These were discussed above. Napp confirmed that the actions of the representative were not in breach of Napp's Code of Business Ethics in respect of his interactions with health professionals. Furthermore, given the evidence above, Napp submitted that the representative's actions whilst interacting with the health professionals, obtaining permission to email them and then arranging for the email to be sent, would or could not be objectively viewed as being unethical in any way. Napp explained that the representative had been dismissed by the agency. Napp also terminated the contract with the agency, however this was related to wider agency contractual and commercial performance matters.

In these incidents the relevant requirements of Clause 9.9 of the Code related to having the prior permission of the recipient to use email for promotional purposes. As explained above, Napp submitted that the representative had complied with this Code requirement in respect of all three incidents.

PANEL RULING

The Panel noted Napp's submission that during a seven month period the agency had recorded over 2,100 calls. However, the Panel disagreed with Napp's description of the three incidents at issue, which all involved the same representative, as 'an isolated and contained episode'. The Panel noted that Napp's investigation into the three incidents had been hampered by the representative's persistent poor record keeping.

The Panel noted that Clause 9.9 stated, *inter alia*, that email communications must not be used for promotional purposes, except with the prior permission of the recipient. In the Panel's view this permission had to be obtained from the recipient of the material and could not be given by a third party on the recipient's behalf. In that regard the Panel noted that an email dated 23 May from one of the agency's sales managers to his sales team clearly stated that email addresses of health professionals given by receptionists and support staff could not be used without direct permission from the recipient.

The Panel considered each incident separately.

1 Practice Manager

The Panel noted that on receipt of emailed, additional BuTrans information, the practice

manager had emailed Napp to inform the company that she had not requested any information, that she did not want to receive any further information and that her email address should be removed from its circulation list. The practice manager referred to the representative by name but did not state whether she had given him her email address. The representative's call notes stated that 'the customer requested med info' but did not state how such information was to be sent. Napp did not know how the representative had obtained the practice manager's email address. The Panel noted that extreme dissatisfaction was generally required before an individual was moved to complain but considered that on the basis of the information before it, it was impossible to know whether the practice manager had given her email address, and her permission to use it for promotional purposes, to the representative. The Panel therefore ruled no breach of Clauses 9.9 and 15.2. Consequently no breach of Clause 9.1 was ruled.

2 Practice Manager

The Panel noted that Napp had emailed the practice manager with additional BuTrans information and that in response the practice manager had stated that she had not had the conversation referred to in the email and queried whether Napp had sent the information to the right person. The Panel noted that Napp's email template referred to a 'recent online conversation' and Napp's submission that the representative had telephoned the practice manager and that this might explain why she could not remember the conversation. The Panel noted Napp's submission that the representative's call logs showed that three calls had been made to the practice in question and although the call notes were not detailed, they stated that information had been requested. The call notes did not state how the information was to be sent but the Panel noted that Napp understood that the representative had stated that he had gained express permission from the practice manager given the previous incident and further instructions from Napp. The Panel further noted Napp's submission that email addresses were not stored in the call system and the original appointment had been made with a different health professional so it was difficult to rule out the possibility that the email address for the practice manager had been obtained during a telephone conversation. As above, the Panel considered that it was impossible to know whether the practice manager had spoken to the representative and given her email address, and her permission to use it for promotional purposes. The Panel therefore ruled no breach of Clauses 9.9 and 15.2. Consequently no breach of Clause 9.1 was ruled.

3 Practice Manager and Doctor

The Panel noted that following receipt of an email about BuTrans, a doctor emailed Napp stating that he had not had an online conversation with the representative as stated in the email and did not wish to receive any information. In subsequent correspondence, the doctor queried how his contact details had been obtained as he had not shared

them. The Panel noted Napp's submission that the practice manager had provided the representative with the doctor's email address and instructed him to send the additional BuTrans material. This was supported by the representative's brief call notes. The Panel noted, however, that in a further email to Napp, the doctor stated that the practice manager had no recollection of any conversation with the representative at issue and that he would not have revealed the doctor's email address in conversation with a representative. The Panel noted Napp's submission that as the doctor used a short form of his name in his email address the representative was unlikely to have been able to guess it and so he must have been given it by someone; it appeared clear, however that that someone was not the doctor. The Panel noted that Clause 9.9 required prior permission from the recipient before emails could be used for promotional purposes; such permission could not be granted by a third party. The Panel considered that the doctor had been emailed promotional

material without his prior permission. A breach of Clause 9.9 was ruled. The Panel considered that the representative had not maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled. High standards had not been maintained and a breach of Clause 9.1 was ruled.

During the consideration of this case the Panel was concerned that the representative's call notes were of a very poor quality and it queried whether more could have been done by Napp and the agency to guide the representative on best practice for completing call notes. The Panel requested that its general concerns were drawn to Napp's attention.

Complaint received

19 July 2013

Case completed

12 September 2013

NOVO NORDISK v SANOFI

Breach of undertaking

Novo Nordisk alleged that a Lyxumia (lixisenatide) press release on Sanofi's website, breached the undertaking given by Sanofi in Case AUTH/2604/5/13.

As the complaint concerned an alleged breach of undertaking, it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The detailed response from Sanofi is given below.

The Panel noted that an undertaking was an important document. Companies had to give an undertaking that the material in question and any similar material, if not already discontinued or no longer in use, would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that Case AUTH/2604/5/13 concerned an advertisement which featured the claims 'Lyxumia leads to even greater costs savings of' and 'Turn to the GLP-1 that minimises costs'. Novo Nordisk had alleged that the claims did not take into account the differences in efficacy and safety between Lyxumia and similar treatments. Sanofi had acknowledged that the claims might imply wider savings beyond the acquisition cost and had committed to amend such claims. However, a press release issued after the completion of inter-company dialogue featured the claim 'Lyxumia is a new, cost-effective option...'. The Panel considered that the term 'cost-effective' clearly implied savings beyond the acquisition cost alone and in that regard inter-company dialogue about the advertisement had been unsuccessful. The Panel had considered that without the benefit of more information, it was not clear that the claims in the advertisement were only based on acquisition costs and not a cost-effectiveness analysis or similar. The Panel considered that the claims were misleading and breaches of the Code were ruled.

In Case AUTH/2604/5/13 when considering the inter-company dialogue, the Panel referred to the press release now at issue in Case AUTH/2619/7/13 noting that it featured the claim 'Lyxumia is a new, cost-effective option'. In Case AUTH/2604/5/13, the Panel disagreed with Sanofi's submission that the press release made no explicit or implicit claim that Lyxumia would achieve 'cost savings' or 'cost minimisation' beyond the cost of the medicine itself. The Panel considered that the term 'cost-effective' clearly implied savings beyond the acquisition cost alone.

The Panel noted Sanofi's submission in Case AUTH/2604/5/13 that it had examined the press release before it was issued to ensure that, as per the company's inter-company commitment, claims, implicit or explicit, for wider savings than the cost of Lyxumia alone were not included.

Turning to the present case, Case AUTH/2619/7/13, the Panel noted that the heading of the press release stated that Lyxumia '... could save the NHS millions offering value and choice'. The first paragraph stated 'costing over 25% less than similar treatments...'. The claim 'Lyxumia is a new, cost-effective option' and 'The price is one that represents real value to both the NHS and Sanofi' appeared in the penultimate and final paragraph respectively. The Panel noted that Sanofi had removed the press release from the press section of its website. The Panel noted Sanofi's detailed account of its review and withdrawal of material which it undertook and completed following resolution of matters during inter-company dialogue and prior to notification of the ruling and provision of the undertaking in Case AUTH/2604/5/13. It appeared that when Sanofi provided its undertaking in Case AUTH/2604/5/13 it did not revisit the decisions it had made when it withdrew material following inter-company dialogue. The Panel was concerned that the press release in question had remained in the press section of the Sanofi website.

The Panel noted that there were differences between the claims at issue in the press release and those previously at issue in the advertisement. However, the Panel considered that neither of the claims at issue cited by Novo Nordisk 'Lyxumia is a new cost effective option' and 'The price is one that represents real value to both the NHS and Sanofi' in the press release made it sufficiently clear that it was based on the acquisition cost of the medicine alone. The term cost-effectiveness implied that indirect costs and efficacy had been taken into account and that was not so. The Panel considered that as the press release did not make it sufficiently clear that the claims in question related solely to the acquisition cost of Lyxumia, they were sufficiently similar to those at issue in Case AUTH/2604/5/13 to be covered by the undertaking in that case. The Panel therefore considered that each claim breached the undertaking previously given and a breach of the Code was ruled. High standards had not been maintained; a further breach of the Code was ruled.

The Panel was concerned that the documents provided to the Authority indicated that only promotional material was examined during the withdrawal of material following successful inter-company dialogue and that Sanofi had not reviewed these initial withdrawal decisions when it provided its undertaking to the Authority. In particular, the

Panel had noted that the press release in question was highlighted in the previous case wherein the similarity of the claims in the press release to those in the advertisement at issue was noted. In these circumstances the Panel was thus very concerned that Sanofi considered that the press release was beyond the scope of the undertaking. The Panel noted that the company's submission in this regard was inconsistent with its submission in Case AUTH/2604/5/13 wherein it stated that it had examined the press release prior to issue to ensure that it adhered to the company's commitment made in inter-company dialogue. The Panel noted its comments above about the importance of compliance with undertakings. The Panel considered that the conduct of Sanofi in this regard had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Novo Nordisk Limited alleged that Sanofi had breached its undertaking given in Case AUTH/2604/5/13.

COMPLAINT

Novo Nordisk noted that in Case AUTH/2604/5/13 it had raised concerns about the use of the following claims in a Lyxumia (lixisenatide) advertisement published in the Health Service Journal:

- 'Lyxumia leads to even **greater cost savings** of'
- 'Turn to the GLP-1 that minimises cost'

During inter-company dialogue Sanofi acknowledged that such cost saving comparisons might invite conclusions beyond acquisition cost alone and agreed to amend such claims. However, further to this commitment, Sanofi issued a press release on 1 May 2013, which featured similar claims to those in the advertisement. Novo Nordisk thus considered that inter-company dialogue had failed and it escalated the matter to the PMCPA.

Novo Nordisk stated that in Case AUTH/2604/5/13, the Panel considered that the inclusion of similar cost saving claims in the press release confirmed that inter-company dialogue had failed and that the complaint could proceed. This was confirmed in a letter dated 17 June 2013 which stated:

'The Panel further noted, however, that a press release which was embargoed until 00.01, Wednesday 1 May featured the claim 'Lyxumia is a new cost-effective option...'. The Panel thus disagreed with Sanofi's submission that the press release made no explicit or implicit claim that Lyxumia would achieve 'cost savings' or 'cost minimisation' beyond the cost of the medicine itself.'

Novo Nordisk noted that whilst it had not engaged in inter-company dialogue with Sanofi about the content of the press release *per se*, it contained claims that were similar to those in the Lyxumia advertisement in the Health Service Journal ie:

- 'Lyxumia is a new, cost effective option' (quotation by named health professional)

- 'The price is one that represents real value to both the NHS and Sanofi' (quotation by Sanofi employee)

Novo Nordisk noted that the press release was still accessible on www.sanofi.co.uk several days after Novo Nordisk was notified that Sanofi had accepted the ruling (9 July 2013) in Case AUTH/2604/5/13. Novo Nordisk understood that the undertaking signed by Sanofi requested that Sanofi no longer used the advertisement subject to the complaint, but also that the undertaking applied to any similar materials in circulation.

Novo Nordisk alleged that Sanofi had continued to make available an item which featured similar claims to those that had been deemed misleading by the Panel in Case AUTH/2604/5/13. Novo Nordisk alleged a breach of Clause 25. Given the seriousness of the matter, Novo Nordisk also alleged breaches of Clauses 2 and 9.1.

RESPONSE

Sanofi noted that Case AUTH/2604/5/13 was about a Lyxumia (lixisenatide) advertisement issued by Sanofi and published in the Health Service Journal in March 2013 (ref GBIE.LYX.13.02.11). Prior to that complaint being made to the PMCPA, Sanofi and Novo Nordisk had participated in inter-company dialogue specifically about the advertisement. During the course of that dialogue, Sanofi agreed on 29 April 2013 to withdraw the advertisement, and all similar items. That was achieved through a review of the active Lyxumia materials within the electronic review system, by reviewing the active items on the iPad catalogue system and through direction issued to Sanofi's creative agency. The advertisement which was the subject of the inter-company dialogue was part of a campaign that had come to an end by 29 April; however, as a result of a thorough review, Sanofi identified additional materials containing similar claims to those within the advertisement at issue. The following detailed actions were undertaken as a result:

- Sanofi's creative agency was advised verbally and in writing of the immediate withdrawal of two advertisements (Lyxumia payor advertisement (ref GBIE.LYX.13.02.11) and Lyxumia clinical advertisement (ref GBIE.LYX.13.02.12) (a copy of the email notification with the agency response was provided). The agency was asked to identify the journals to which these items had been submitted as part of Sanofi's advertising schedule and advised that no further submissions be made with these items. Sanofi stated that it had confirmed a new brief for a revised advertisement which did not include the claims concerned.
- A range of 'payor' materials were identified for withdrawal including 'awareness mailers'. These were all head office-led initiatives and the materials were withdrawn with no need to involve the sales force. The items were withdrawn from the electronic review system by the originator, or (as one of the originators was

no longer in the company) via direct request to electronic review system company's staff.

- A leavepiece (ref GBIE.LYX.13.01.14), similar to the advertisement at issue was identified for withdrawal. Following internal discussion, an acceptable timeframe was agreed to withdraw this item. Regardless of the fact that this piece was not the subject to the agreement during inter-company dialogue, a timeframe of two weeks was set. A revised leavepiece was produced (ref GBIE.LYX.13.04.14) which fully met the terms of the inter-company agreement. Given that this involved material in circulation with a sales force, the following detailed actions were taken to ensure the complete withdrawal of the leavepiece and replacement with the revised item:
 - 29 April: A brief for developing the revised leavepiece was provided to the creative agency.
 - 9 May: The sales force was notified that the leavepiece would be withdrawn from use on 13 May, and was briefed on the process for returning the item; members of the sales force were required to return signed declaration forms confirming their actions (signed declarations were subsequently returned and logged).
 - The sales force was provided with a briefing document which explained the changes incorporated in the revised leavepiece (ref GBIE.LYX.13.04.14) (email provided).
 - 9 May: Sanofi distribution centre was advised on the need to quarantine and destroy the original leavepiece (ref GBIE.LYX.13.01.14) (email provided). It was advised of the timeframe for the despatch of the revised leavepiece (ref GBIE.LYX.13.04.14) to the sales force.
 - 12 May: Distribution centre confirmed that the withdrawn items had been quarantined (email provided).
 - 23 May: Distribution centre confirmed that the withdrawn items (including returns from the field) were queued for destruction (email provided).

To manage these actions efficiently, a log of all the resulting unscheduled work was initiated and maintained. This was recorded in an internal web-based workspace ('eRoom') to support transparency across the team that worked on the brand (a copy of the unscheduled work log from the eRoom was provided).

In summary, as a result of inter-company dialogue, Sanofi had removed the advertisement and all similar material, before the case was referred to the Panel, in the same manner and using the same processes as if it had been the subject of an undertaking made to the PMCPA.

Following the Panel's review and notification to Sanofi of its findings in Case AUTH/2604/5/13, Sanofi signed a written undertaking dated 25 June 2013 in which it accepted the decision of the Panel and undertook that 'Use of the advertisement in question and any similar material, if not already discontinued

or no longer in use, will cease forthwith'. When Sanofi signed the undertaking, the actions as detailed above had been completed. Furthermore, Sanofi had not issued any further advertisements or similar promotional items containing the claims that were at issue in this case. Sanofi noted that in the current complaint (Case AUTH/2619/7/13) about the alleged breach of undertaking, Novo Nordisk did not submit any evidence that Sanofi had issued or continued to use any advertisement or similar promotional item containing the claims at issue.

Sanofi noted that Novo Nordisk had alleged a breach of undertaking because 'Sanofi has continued to make available an item **which contains similar claims as those which have been deemed misleading ...**'.

Sanofi noted that its signed undertaking explicitly referred to 'Use of the advertisement in question and any similar material ...'. The undertaking did not refer to any specific claim or claims.

Sanofi acknowledged that the press release (ref GBIE.LYX.13.03.12) was accessible in the press section of its website (www.sanofi.co.uk) when Novo Nordisk stated it was and as demonstrated in its letter by way of a screen shot. Sanofi stated that the press release had been examined and approved within its validated approval system (Zinc) for use as a press release and was issued once (30 April 2013) to health journalists of national and regional newspapers and to pharmaceutical trade press. This was the only occasion and the only purpose for which it was used, but it was subsequently placed in the press section of the Sanofi website. Following the initial use as described above, the press release had only ever been accessible in the press section of the Sanofi website. It was not distributed or available in any other format or medium. In particular, it had never been submitted for publication as an advertisement or been distributed in any promotional medium.

Sanofi considered that a press release, which was examined and used as such in full compliance with the Code, could not be considered to be an advertisement or similar material. An advertisement and similar material would be certified as promotional material in accordance with Clause 14 and would be proactively distributed through a variety of appropriate promotional channels in accordance with the use for which it was certified. By its very nature, a press release was inherently dissimilar to an advertisement and similar promotional material. In that regard, and because the undertaking was not to use the advertisement and any similar materials, Sanofi did not consider that the availability of the press release constituted a breach of the undertaking. The company denied breaches of Clauses 25, 9.1 and 2. However, to demonstrate its commitment to conclude this issue, Sanofi stated that it had removed the press release from its website when it received the complaint about it.

Sanofi noted that it had not engaged in inter-company dialogue with Novo Nordisk on the subject of any press release (as confirmed by Novo Nordisk in its complaint). Sanofi recognised that the content of the press release was referred to in Case

AUTH/2604/5/13; however, it noted that this was in the context of whether that case should proceed and that the final Panel ruling on the claims at issue were explicitly referenced to the advertisement. The first notification Sanofi received about the ongoing availability of the press release was when it was notified of this complaint. Given that the lack of inter-company dialogue on the press release, Sanofi submitted that it would have been more constructive and in keeping with both the spirit and letter of the Code for Novo Nordisk to raise this as a new issue directly with Sanofi as soon as it had identified it, enabling the issue to be resolved through inter-company dialogue without the need for recourse to the PMCPA.

PANEL RULING

The Panel noted that an undertaking was an important document. Companies had to give an undertaking that the material in question and any similar material, if not already discontinued or no longer in use, would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the undertaking was not limited to promotional material as inferred by Sanofi; it covered all similar materials irrespective of their promotional status including press releases and such like.

The Panel noted Sanofi's comments about the absence of inter-company dialogue on this matter. The Panel noted that Paragraph 5.3 of the Constitution and Procedure provided that the requirements for inter-company dialogue did not apply where the allegation was that a company had failed to comply with its undertaking and was in breach of Clause 25 of the Code. Novo Nordisk was therefore not required to engage in inter-company dialogue on this matter.

The Panel noted that the previous case, Case AUTH/2604/5/13, concerned an advertisement which, *inter alia*, featured the claims 'Lyxumia leads to even greater costs savings of' and 'Turn to the GLP-1 that minimises costs'. Novo Nordisk had alleged, *inter alia*, that whilst the claims in question were correct when the pack price of Lyxumia was compared to the pack price of similar treatments, this comparison did not take into account the differences in efficacy and safety between Lyxumia and similar treatments. Sanofi had acknowledged that the claims might imply wider savings beyond the acquisition cost and had committed to amend such claims. The Panel had considered that without the benefit of more information, it was not clear that the claims in the advertisement were only based on acquisition costs and not a cost-effectiveness analysis or similar. The claims were considered to be misleading and breaches of Clauses 7.2 and 7.3 were ruled.

In Case AUTH/2604/5/13 when considering the inter-company dialogue, the Panel referred to the press release now at issue in Case AUTH/2619/7/13 noting that it featured the claim 'Lyxumia is a new, cost-

effective option'. The press release had been issued after the completion of inter-company dialogue. In Case AUTH/2604/5/13, the Panel disagreed with Sanofi's submission that the press release made no explicit or implicit claim that Lyxumia would achieve 'cost savings' or 'cost minimisation' beyond the cost of the medicine itself. The Panel had considered that the term 'cost-effective' clearly implied savings beyond the acquisition cost alone.

The Panel noted Sanofi's submission in Case AUTH/2604/5/13, that it had examined the press release currently at issue, before it was issued to ensure that as per the company's commitment in inter-company dialogue claims in the advertisement which implied wider savings than the cost of the medicine alone were not used. Further that no explicit nor implicit claim that Lyxumia would achieve cost savings or cost minimisation beyond the cost of the medicine itself was made.

Turning to the present case, Case AUTH/2619/7/13, the Panel noted that the press release was headed 'Lyxumia (lixisenatide) – effective new Type 2 diabetes treatment could save the NHS millions offering value and choice'. The first paragraph stated 'costing over 25% less than similar treatments...'. The claims cited by Novo Nordisk 'Lyxumia is a new, cost-effective option' and 'The price is one that represents real value to both the NHS and Sanofi' appeared in the penultimate and final paragraph respectively. The Panel noted that Sanofi had now removed the press release from the press section of its website. The Panel noted Sanofi's detailed account of its review and withdrawal of material which it undertook and completed pursuant to resolution of matters during inter-company dialogue and prior to notification of the ruling and provision of the undertaking in Case AUTH/2604/5/13. It appeared that Sanofi had not validated the decisions made during its withdrawal process pursuant to inter-company dialogue when providing its undertaking in Case AUTH/2604/5/13 dated 25 June 2013. The Panel was concerned that the press release in question had remained in the press section of the Sanofi website.

The Panel noted that there were differences between the claims at issue in the press release and those previously at issue in the advertisement. However, the Panel considered that neither of the claims at issue cited by Novo Nordisk 'Lyxumia is a new cost effective option' and 'The price is one that represents real value to both the NHS and Sanofi' in the press release made it sufficiently clear that it was based on the acquisition cost of the medicine alone. Indeed, the term cost-effectiveness implied that indirect costs and efficacy had been taken into account and that was not so. The Panel considered that on the basis that the press release did not make it sufficiently clear that the claims in question related solely to the acquisition cost of the medicine, the claims at issue were sufficiently similar to those at issue in Case AUTH/2604/5/13 to be covered by the undertaking in that case. The Panel therefore considered that each claim breached the undertaking previously given. A breach of Clause 25 was ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel was concerned that the documents provided to the Authority indicated that only promotional material was examined during the withdrawal of material pursuant to successful inter-company dialogue. The Panel was also concerned that Sanofi had not reviewed these initial withdrawal decisions when it provided its undertaking to the Authority. In particular, the Panel noted that the press release in question was highlighted in the previous case wherein the similarity of the claims in the press release to those in the advertisement at issue was noted. In these circumstances, the Panel was very concerned that Sanofi considered that the press release was beyond the scope of the undertaking. The Panel noted that the company's submission in this regard was inconsistent with

its submission in Case AUTH/2604/5/13 wherein it stated that it had examined the press release prior to issue to ensure that it adhered to the company's commitment made in inter-company dialogue. The Panel noted its comments above about the importance of compliance with undertakings. The Panel considered that the conduct of Sanofi in this regard had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received

22 July 2013

Case completed

10 September 2013

ANONYMOUS v BAYER

Provision of Hospitality

An anonymous, non-contactable health professional complained about the provision of hospitality by Bayer at an international congress held in Amsterdam. The complainant alleged that a senior Bayer employee had entertained two health professionals in a hotel bar during the early hours of the morning and it looked as though significant amounts of alcohol had been consumed.

The detailed response from Bayer is given below.

The Panel noted from Bayer's account that on the evening in question its global colleagues had organized a dinner for researchers who had won scholarships under a Bayer awards programme. Three UK health professionals invited to the dinner had then walked the Bayer employee back to her hotel to save her walking alone and also because the closest taxi rank was situated outside her hotel. The Panel noted that according to Bayer the Bayer employee had purchased 4 drinks, one for each member of the group, at a cost of £28.15 just before midnight while waiting for the health professionals' taxi to arrive. The Panel did not know what type of drinks had been purchased. Bayer had not provided details. Purchase of alcoholic drinks would not be in line with Bayer's standard operating procedure. The drinks in the hotel bar were in addition to the hospitality already provided that evening. The Panel did not know if the group knew how long the taxi would be or how long it took to arrive. The Panel did not know why the group had not picked up a taxi at the dinner venue. The Panel considered that the circumstances in this case were exceptional. Nonetheless it was important for a company to be mindful of the impression created by its activities; this was especially so in relation to the provision of drinks late at night in a public bar irrespective of the circumstances. The Panel did not consider that drinks (particularly as they were likely to be alcoholic) in these circumstances constituted subsistence as outlined in the Code and a breach was ruled. The Panel did not consider that, given the exceptional circumstances of this case, high standards had not been maintained and no breach of the Code was ruled.

An anonymous, non-contactable health professional complained about the provision of hospitality by Bayer plc at the International Society on Thrombosis and Haemostasis (ISTH) Congress held in Amsterdam 29 June – 4 July 2013.

COMPLAINT

The complainant stated that as a health professional he/she was aware of the Code and its importance in governing the behaviour of pharmaceutical companies at meetings and congresses. With that in mind the complainant considered it necessary, after much deliberation, to report an incident he/she had

observed at the recent ISTH Congress.

The complainant stated that on returning to his/her hotel he/she observed a senior member of the Bayer group entertaining two of his/her eminent consultant colleagues in the early hours of the morning, in the hotel bar. It looked as though significant amounts of alcohol were being consumed.

The complainant considered that, as he/she had previously been told by the other members of the Bayer group that nightcaps were strictly forbidden by the company, the Code might have been breached. The complainant thus considered that he/she must report this incident and hoped that the person in question would be reprimanded.

When writing to Bayer, the Authority asked it to consider the requirements of Clauses 9.1 and 19.1 of the Code.

RESPONSE

Bayer submitted that its global arm held an awards dinner for researchers from around the world who had won scholarships under the Bayer Haemophilia Awards Programme (BHAP) on July 1 during the ISTH congress in Amsterdam. Three UK health professionals were invited to the dinner. The company provided reasons for their attendance; all had links to the awards programme. They were escorted to the dinner by a senior Bayer UK employee.

Bayer stated that the three UK health professionals stayed in different hotels in the city centre and not in the Bayer chosen hotel. Two of the health professionals worked for Bayer plc under full contract; one of them was also supported financially to attend the congress.

The Bayer employee stayed at a hotel which was approximately a 15 minute walk from the evening venue but in a quiet part of the city. At the end of the evening, approximately 23.30 hours, the health professionals walked the Bayer employee back to her hotel to save her walking alone and also because the closest taxi rank was outside of her hotel.

When the group arrived at the hotel there were no taxis available. They asked the doorman to ring for a taxi and he informed them that it would take some time to arrive. They decided to wait inside the hotel lobby bar and have a drink. It was nearly midnight. Four drinks were purchased, one for each member of the group, at a cost of £28.15. The hotel lobby bar was open to other residents which might have included members of the public.

An invoice from the hotel was provided which showed one amount for all food and beverage

purchased on the day in question, at a cost of €114.50 (itemised invoices were not provided by the hotel). Earlier in the day the Bayer employee had met with her team to plan out activities for the remainder of the meeting, and also just prior to them leaving for a separate dinner. On both occasions she had purchased drinks for them which made up the remainder of the amount shown on the hotel invoice. Bayer submitted that the employee in question had passed her ABPI Representative's Examination with distinction.

PANEL RULING

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

Clause 19.1 stated that hospitality must be strictly limited to the main purpose of the event and must be secondary to the purpose of the meeting ie subsistence only. The level of subsistence offered must be appropriate and not out of proportion to the occasion. The supplementary information to Clause 19.1 made it clear that the provision of hospitality was limited to refreshments/subsistence (meals and drinks), accommodation, genuine registration fees and the payment of reasonable travel costs which a company might provide to sponsor a delegate to attend a meeting. In determining whether a meeting was acceptable or not consideration needed to be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, subsistence provided and the like. It should be the programme that attracted delegates and not the associated hospitality or venue. The supplementary information also stated that a useful criterion in determining whether the arrangements for any meeting were acceptable was to apply the question 'would you and your company be willing to have these arrangements generally known?' The impression that was created by the arrangements for any meeting must always be kept in mind.

The Panel noted that in addition to the requirements in the Code regarding meetings and the provision of hospitality companies were required to have a written document setting out their policies on meetings and hospitality and associated allowable expenditure. The Panel noted that company policies and procedures had to be in line with the Code. A company's policies might be more restrictive than the Code. The Panel noted the complainant's submission that he/she had previously been told by other members of the Bayer group that nightcaps were strictly forbidden by the company.

The Panel noted that the Bayer SOP Meetings Policy (BHC-BP-UK-SOP-101) stated that drinks other than reasonable amounts of soft drinks, water, coffee and tea must not be provided after a meal.

The Panel noted that the complainant had alleged that a senior Bayer employee had entertained two of his/her colleagues during the earlier hours of the morning in the hotel bar and it looked as though significant amounts of alcohol had been consumed. The Panel noted that the complainant had not specified the name of the hotel or the date of the alleged incident. The Panel noted that as the complainant was non-contactable, it could not confirm that the subject of his/her complaint was the incident referred to by Bayer.

The Panel noted that Bayer had provided an account of the evening of 1 July when following an awards dinner organised by its global colleagues for researchers from around the world who had won scholarships under the Bayer Haemophilia Awards Programme, three UK health professionals that were invited to the dinner had walked the Bayer employee back to her hotel to save her walking alone and also because the closest taxi rank was situated outside her hotel. The health professionals included two who worked for Bayer plc under full contract; one of them was also supported financially to attend the congress.

The Panel noted that according to Bayer its employee had purchased four drinks, one for each member of the group, at a cost of £28.15 just before midnight while waiting for the health professionals' taxi to arrive. This was supported by the employee's expense claim, a copy of which was provided. The Panel did not know what type of drinks had been purchased. Bayer had not provided details. Purchase of alcoholic drinks would not be in line with Bayer's SOP. Unfortunately the hotel did not supply itemised invoices and so the invoice provided by Bayer showed one amount for all food and beverage purchased on the day in question, at a cost of €114.50 and included drinks purchased by the employee for her team earlier in the day. The drinks in the hotel bar were in addition to the hospitality already provided that evening. The Panel did not know whether the doorman had indicated precisely how long the group would have to wait for a taxi nor did it know how long the taxi took to arrive. The Panel did not know why the group had not picked up a taxi at the dinner venue.

The Panel considered that the circumstances in this case were exceptional. Nonetheless it was important for a company to be mindful of the impression created by its activities; this was especially so in relation to the provision of drinks late at night in a public bar irrespective of the circumstances. The Panel did not consider that drinks (particularly as they were likely to be alcoholic) in these circumstances constituted subsistence as outlined in Clause 19.1. A breach of Clause 19.1 was ruled. The Panel did not consider that, given the exceptional circumstances of this case, a ruling of a breach of Clause 9.1 was warranted and no breach of that clause was ruled.

Complaint received

26 July 2013

Case completed

30 August 2013

NHS EMPLOYEE v SANOFI

Conduct of representative

An NHS clinical commissioning group employee complained that a Sanofi representative had persuaded an NHS employee to send, on his/her behalf, a promotional email via the NHS.net system to all GP practices in the area. The email invited recipients to view a Sanofi promotional webcast.

The detailed response from Sanofi is given below.

The Panel noted that the email sent by the administrative assistant on behalf of the Sanofi representative had a subject heading of 'FW:Sanofi GLP-1 Webcast'. The email itself was headed 'Sent on behalf of [named representative] – Sanofi Practice Managers- please cascade'. The email, signed by the representative as a 'Diabetes Specialist' (although the company was not stated), was an invitation to a webcast entitled 'The Use of GLP-1 receptor agonist therapies, the evidence and practicalities'. In the Panel's view it was not clear from the email that the webcast was promotional or that it had been solely produced by Sanofi. The email was sent via the NHS.net system and stated that 'We are holding a webcast entitled...'. It could be argued that the impression given was that the meeting was an NHS-led meeting with sponsorship from Sanofi and not a Sanofi-led promotional meeting. The Panel noted that although the email did not refer to the meeting as an NHS meeting, it was likely to appear to recipients that the NHS trust endorsed the meeting as it had been sent from an NHS employee who regularly sent out details of workshops and courses that the local community healthcare trust had organised. It was only on clicking the registration link that the promotional nature of, and Sanofi's involvement with, the webcast was made clear. The Panel considered that the invitation disguised the promotional nature of the webcast and in that regard a breach of the Code was ruled. The Panel also ruled a breach of the Code as acknowledged by Sanofi as prior permission to send the promotional email had not been obtained from those who received it.

The Panel noted that by sending the email in question, the representative had, in effect, created and distributed his/her own promotional material; the email had not been certified prior to use in accordance with the Code. The Panel considered that the representative had thus failed to maintain high standards. A breach of the Code was ruled.

The Panel noted that the representative had persuaded an NHS administrative assistant to widely distribute an email on his/her behalf. The Panel considered that this was a serious breach of professionalism and that in doing so the representative had failed to maintain a high standard of ethical conduct. The representative had also failed to comply with all the relevant

requirements of the Code. A breach of the Code was ruled as acknowledged by Sanofi.

The Panel considered that the representative's conduct was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

An NHS clinical commissioning group employee complained that a Sanofi representative had persuaded an NHS employee to send, on his/her behalf, a promotional email via the NHS.net system to all GP practices in the area. The email invited recipients to view a Sanofi promotional webcast by logging on from their own PC or attending a viewing of it at a specific venue and provided registration details.

COMPLAINT

The complainant alleged that the activities of a Sanofi representative breached Clause 9.9 and brought the industry into disrepute by misusing contact with an NHS employee.

The complainant provided a copy of an email which the Sanofi representative had persuaded an administrative assistant in the local community healthcare trust to circulate to every GP and practice in the area via the NHS.net system; this imbued the content with unwarranted 'official' NHS endorsement. The complainant suspected that the member of staff might have mistakenly thought that the educational event in question was similar to the official in-house training provided within the trust. The complainant was interested to know how clear the representative made it that this was not so.

The complainant stated that no promotional material should be sent without the express permission of the recipient, let alone under the guise of an official NHS organisation. Whilst the meeting purported to be an educational webcast, given the recent launch of Lyxumia (lixisenatide), the complainant did not believe it unreasonable to regard this as a rather cynical promotional exercise. Indeed, on following the links within the email a screen appeared and confirmed the promotional nature of the webcast. The complainant provided a copy of the link.

The head of clinical governance for the local community healthcare trust investigated the incident and reported that:

'The member of staff is an administrator in the community diabetes office and she regularly sends out details of workshops and courses the local community healthcare trust have organised internally city-wide. On this occasion the information came from a representative

from Sanofi and rather than reading the detail beforehand she inadvertently sent it out. At the time she was the only person in the office so had not been able to check with someone if it was OK to send out. She did not question why the representative had asked her to circulate this on her behalf. Following a query from a GP she immediately recalled the email but it still reached some individuals. At the time she did not send out an apology or advice to ignore the email as this would have compounded the issue of "junk" mail. She said she sent this out in error. She has since spoken to the representative from Sanofi who has apologised to her for making this request in the first place. She made her line manager aware, completed an incident report, and knows in future not to send anything out without authorisation. I have since spoken to the line manager who has reassured me that the member of staff will not make the same mistake twice'.

The complainant subsequently received a follow up email which stated:

'The member of staff is very upset, and the representative did apologise'

The complainant did not consider that the representative's apology was adequate. The complainant found it reprehensible that a member of the pharmaceutical industry played upon the good nature and lack of knowledge of a non-clinical colleague to arrange for promotional material to be distributed to GPs and practice staff via NHS email. The complainant did not believe that any representative could be unaware that this was unacceptable.

This had resulted in a great deal of upset for an administrative employee who should never have been put in this position and found herself being investigated by the head of clinical governance in her employing organisation.

The complainant provided a copy of the email trail containing the original email at issue.

When writing to Sanofi, the Authority asked it to respond in relation to Clauses 2, 9.1, 9.9, 12.1 and 15.2.

RESPONSE

Sanofi submitted that it took its responsibilities under the Code extremely seriously and was concerned to have received a complaint of this nature; the matter had been investigated by the medical director and the line manager of the representative in question.

The activity in question was the use of NHS email systems to invite health professionals to attend a Sanofi-organised promotional meeting. Before addressing the specifics of the allegation itself Sanofi submitted that it was helpful to understand the meeting to which it related and the procedures which had been established to ensure that invitations were

handled in an appropriate fashion and in compliance with the Code.

Sanofi organised a scientific symposium at the 2013 Diabetes UK Professional Meeting to present information on its new glucagon-like peptide-1 (GLP-1) receptor agonist, lixisenatide. Although scientific in content, the meeting was promotional and all content and materials were therefore reviewed and approved following Sanofi's standard operating procedure (SOP) according to the requirements of the Code.

To allow wider dissemination of the information after the Diabetes UK Professional Meeting, the speakers were filmed as they presented. The resulting talking head videos were combined with their on-screen information to produce an audio-visual presentation. This was delivered as a promotional webcast on 3 July 2013, with the pre-recorded speakers available on-line to answer questions raised by the audience who viewed the programme at remote locations. Again, the content of this presentation was reviewed and approved following Sanofi's SOP, as was the briefing material to the speakers (to ensure that questions raised by the audience were handled according to the requirements of the Code).

Sanofi representatives could arrange local meetings at which clinicians could view the webcast, facilitated by the representative. They were also able to provide support (in registration and ensuring access to the webcast system) to individual clinicians who chose to view the webcast on their own equipment.

A comprehensive staff briefing package was developed to ensure that the representatives managed all elements of the delivery of remote meetings in a compliant manner, again with all invitations and briefing materials reviewed and approved according to Sanofi's SOP. The elements relating to invitation of health professionals to local meetings comprised:

- an email invitation provided only to the agency hosting the event, which was sent, specifically, only to those health professionals who had agreed to receive promotional information electronically. (Sanofi recognised that this was not the invitation that was sent by the representative that had given rise to the allegation)
- a hard copy invitation that was to be mailed from Sanofi head office to key customers who had not provided permission to be contacted electronically.
- a hard copy invitation provided to the Sanofi sales teams to invite other customers not already invited above. This was, by intent, the only material provided to the sales force to be used with health professionals as an invitation to the meeting.

The briefing materials then described the procedures to be followed by representatives to allow successful connection to the on-line meeting where this was

delivered by Sanofi staff, and to support individual health professionals to register and access the meeting if they had joined as individual attendees.

To reinforce the importance of compliance, the sales force was briefed both in writing and through an audio-visual presentation, copies of each were provided.

Sanofi submitted that at all stages in the development of the concept and content of the meeting, the process for inviting attendees and delivering meetings locally, and in the briefing of relevant Sanofi employees on how to do so, its internal procedures were followed appropriately and all elements of the programme met the high standards required by the Code. In particular, a special emphasis was placed on only inviting by email those health professionals who had given permission to be contacted in this way.

With respect to these processes, Sanofi therefore considered that the company had demonstrated high standards throughout.

The events relating to the complaint at issue had been clarified by the investigation. It was clear that the record provided by the complainant was an accurate summary of events and no element of this was contested. The key points confirmed by the investigation were set out below:

The representative, who was experienced, had passed the ABPI Medical Representatives Examination and had been employed by Sanofi for a number of years, wrote an email invitation (as provided by the complainant) of his/her own and provided this to the NHS member of staff. This was clearly contrary to Sanofi's SOP whereby all arrangements and materials for local meetings required manager review and approval before use. Review was not sought, nor would approval have been granted. The representative recognised that he/she had failed to follow company processes, and clearly understood that to have asked an NHS employee to email an invitation to a promotional meeting without the approval of recipients failed to meet the standards required of Sanofi and of the Code.

Although not providing any degree of mitigation, the representative had explained that she followed this course of action as he/she believed that the meeting was of true educational value and would have been of significant interest to the audience, and was keen to ensure that the local practitioners were aware of it before he/she went on annual leave 2 days later. The representative did not want the health professionals to miss the opportunity of attending the meeting if they considered it of value to do so.

The representative had a long-standing, convivial relationship with the NHS staff member and it was clear that he/she was overly-dependent on the nature of this relationship when he/she progressed the arrangements for the meeting. This was self-evident from the nature of the email exchange. In retrospect,

the representative acknowledged that a more professional approach should have been adopted, and that consideration of the NHS staff member's position and responsibilities was also necessary.

Immediately upon being made aware of the complaint, the representative spoke to the NHS employee who had sent the email on his/her behalf and offered her a personal and unreserved apology, recognising the importance of the event to the individual.

In summary, it was clear from the investigation that both the health professional and Sanofi had been let down by the actions of one employee who, despite his/her experience, failed to follow established Sanofi procedures. This resulted in an NHS staff member, acting on behalf of the representative, emailing an invitation to a promotional meeting without the prior approval of the recipients. Sanofi acknowledged that this failed to meet the requirements of Clause 9.9.

Furthermore, the invitation failed to make it sufficiently clear that the meeting was promotional. Sanofi acknowledged that this failed to meet the requirements of Clause 12.1.

Each of these individual courses of action showed that the representative failed to demonstrate the high standards required of his/her role, which Sanofi acknowledged was in breach of Clause 15.2.

Sanofi submitted that in the development and execution of this programme all relevant processes were followed in full by all staff aside from the individual in question. This complaint had arisen as a result of the unprompted actions of the individual alone, who had admitted that he/she acted with a degree of naivety unexpected for his/her position. Robust briefings were constructed and delivered to all staff engaged in this project. In particular, the use of electronic communication was given special consideration from the outset, with a clear understanding between Sanofi and the provider agency at conception of the project that promotional emails would be sent only to those who had opted-in to receiving such material. Hard-copy printed invitations were the only material provided to the sales team to be used to invite health professionals.

On balance, Sanofi therefore submitted that although the representative's actions fell well below the standards expected, the organisation did its utmost to maintain the high standards that it set at the company-wide level. Sanofi submitted that it therefore met the requirements of Clause 9.1 and that no breach had occurred in that respect.

These events had triggered a disciplinary process, as per Sanofi's SOP. More comprehensively, a company-wide training update on the requirements of the Code was to be delivered within the third quarter of 2013. This complaint had reinforced the importance of emphasising the requirements around communicating electronically, and this would be given due prominence within the programme.

Sanofi submitted that the processes it had in place were robust, that the approved arrangements for content and delivery of the programme met all the requirements of the Code and if followed would have prevented this complaint arising; it had taken appropriate action at the individual and company-wide level in response to the events that had happened. Sanofi aspired to be a fully compliant organisation and aimed to meet all the high standards required of the Code and to continue to reinforce these. On this basis, Sanofi submitted that a ruling of a breach of Clause 2 would be disproportionate.

Sanofi concluded that it recognised that the actions that occurred were in breach of Clauses 9.9, 12.1 and 15.2. However it disagreed that the actions of the individual implied that the company failed to maintain high standards, nor reflected a need for the organisation to require particular censure.

PANEL RULING

The Panel noted that the email at issue was sent by the representative when he/she was about to go on holiday. A statement from the representative (copy provided by Sanofi) stated that interest in the meeting where Sanofi would be showing the webcast was low and the team subsequently cancelled the meeting.

The Panel noted that the email sent by the administrative assistant on behalf of the Sanofi representative had a subject heading of 'FW:Sanofi GLP-1 Webcast'. The email itself was headed 'Sent on behalf of [named representative] – Sanofi Practice Managers- please cascade'. The email, signed by the representative as a 'Diabetes Specialist' (although the company was not stated), was an invitation to a webcast entitled 'The Use of GLP-1 receptor agonist therapies, the evidence and practicalities'. In the Panel's view it was not clear from the email that the webcast was promotional or that it had been solely produced by Sanofi. The email was sent via the NHS.net system and stated that 'We are holding a webcast entitled....'. It could be argued that the impression given was that the meeting was an NHS-led meeting with sponsorship from Sanofi and not a Sanofi-led promotional meeting. The Panel noted that although the email did not refer to the meeting as an NHS meeting, it was likely to appear to recipients that the NHS trust endorsed the meeting as it had been sent from an NHS employee who regularly sent out details of workshops and courses that the local community healthcare trust had organised. It was only on clicking the registration link that the promotional

nature of, and Sanofi's involvement with, the webcast was made clear. The Panel considered that the invitation disguised the promotional nature of the webcast and in that regard it ruled a breach of Clause 12.1 as acknowledged by Sanofi. The Panel also ruled a breach of Clause 9.9 as acknowledged by Sanofi as prior permission to send the promotional email had not been obtained from those who received it.

The Panel noted that by sending the email in question, the representative had, in effect, created and distributed his/her own promotional material; the email had not been certified prior to use in accordance with Clause 14. The Panel considered that the representative had thus failed to maintain high standards. A breach of Clause 9.1 was ruled.

The Panel noted that the representative had persuaded an NHS administrative assistant to widely distribute an email on his/her behalf. The Panel considered that this was a serious breach of professionalism and that in doing so the representative had failed to maintain a high standard of ethical conduct. The representative had also failed to comply with all the relevant requirements of the Code. A breach of Clause 15.2 was ruled as acknowledged by Sanofi.

The Panel considered that the representative's conduct was such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

During the consideration of this case, the Panel was concerned about the unprofessional nature of the email correspondence between the representative and the NHS administrative assistant. The Panel noted that the Authority had previously issued guidance on the use of emails in which it noted that they were generally regarded as less formal than traditional letters and often casual language was used. If company staff emailed a health professional, appropriate administrative staff or others about a matter which related to their professional role then they should take great care to ensure that the email did not breach the Code through the use of exaggerated claims, immoderate language and the like. A practical rule of thumb might be that if the message could not be sent on company headed notepaper, then it should not be sent by email.

Complaint received

30 July 2013

Case completed

17 September 2013

ANONYMOUS v TAKEDA

Promotion of Rienso

An anonymous, non-contactable complainant complained about a journal advertisement for Rienso (ferumoxytol), issued by Takeda, and the website (www.anaemiazone.co.uk) referred to within it. Rienso was indicated for the intravenous (IV) treatment of iron deficiency anaemia in adults with chronic kidney disease (CKD). Patients were treated with one or two IV doses of 510mg depending on their pre-treatment status. Rienso particles consisted of a bioactive iron oxide core protected by a polyglucose sorbitol-carboxymethylether (PSC) coating.

The complainant noted that the advertisement described Rienso as 'high dose' but did not state what this was in comparison to. The complainant stated that Monofer (iron (III) isomaltoside 1000) could be given at doses of 500mg in haemodialysis patients, and 20mg/kg otherwise, Rienso appeared to be low dose.

The detailed response from Takeda is given below.

The Panel noted that Takeda submitted that 'high dose' was used in conjunction with 'Short course' and 'Rapid bolus injection' to describe the attributes of Rienso's administration and was not used comparatively. The Panel did not consider that the use of 'high dose' in this context was a hanging comparison. No breach of the Code was ruled. With regard to the complainant's further allegation that, compared with Monofer, Rienso appeared to be low dose, the Panel noted that literature provided by Takeda described high dose iron as doses greater than 200mg in a one month period. In the Panel's view the description of Rienso as high dose was supported by the literature. The Panel ruled no breach of the Code.

The complainant noted that the website described Rienso was described as a new IV iron whereas it had been available for over a year. The website stated that both the structure was designed to allow rapid administration of high doses. The complainant alleged that this was unlikely because Rienso appeared to cause more side effects than other IV irons especially immunological reactions and that the high dose was also incorrect. Section 3 stated that Monofer took five injections for 1g whereas it only took two. Section 3 further stated that all IV irons were contraindicated in hypersensitivity to Rienso or other iron preparations. The complainant alleged that this was only true for Rienso. The complainant further alleged that the cost effectiveness section was misleading and unfair because it only took into account the cost of the medicine and not the administration cost. The complainant alleged that the claim that Rienso was convenient was debatable in non haemodialysis patients as three other preparations only required

one infusion. Finally, the cost-competitive statement was repeated although only the medicine cost was referred to.

The Panel noted that the Rienso SPC listed 15 June 2012 as the date of first authorization. The Panel further noted Takeda's account of its activities subsequent to that date and its submission that Rienso could not have been promoted before 8 August 2012 as this was when product training was completed. The Panel noted, however, that a contract between an agency and Takeda stated that '[the agency] would carry out and perform the services...' with effect from the commencement date... ie from 23 July. The services included navigating the changing NHS in the correct timelines with the correct information (advanced product notification (APN) and budget impact model) to ensure appropriate local product update. Reference was made to engaging the right decision makers in a local health economy and key opinion leader advocacy at launch. The advanced product notification referred to budgetary conversations that would take place with relevant NHS budget holders from 23 July but given that this was 5-6 weeks after Rienso had received its marketing authorization, the Panel considered that such activity was promotional. In that regard Rienso had thus been promoted since 23 July 2012 and so could not be described as 'new' beyond 22 July 2013. The Panel however, that the product had been described as new on the website until 1 August 2013. A breach of the Code was ruled.

The Panel noted the complainant's view that the site stated the structure was designed to allow rapid administration of high dose but that seemed unlikely since Rienso appeared to cause more side effects than other IV irons (especially immunological reactions). The Panel understood the complainant to mean that as Rienso caused more side effects than other IV irons (especially immunological reactions) it was unlikely that the structure was designed to allow rapid administration of a high dose. The complainant did not provide any evidence to support this allegation. The Panel noted that the website stated that 'The unique structure of Rienso is designed to allow rapid administration of high doses (510mg) of iron'. A bullet point below stated that the protective PSC coating acted as a shield to reduce immunological sensitivity and release of free iron. The Panel noted that the Rienso SPC stated that in clinical trials, serious hypersensitivity or hypotensive reactions to Rienso were uncommon (reported in 3 (0.2%) of patients with CKD). The Panel further noted that all of the IV iron SPCs provided by Takeda stated that parenteral administration of all iron complexes might cause immediate severe and potentially lethal hypersensitivity reactions. In the Panel's view no

evidence was provided to support the allegation that Rienso caused more side effects than other IV irons (especially immunological reactions). The Panel noted that according to the SPC, Rienso was administered as an undiluted IV injection delivered at a rate of up to 1ml/sec (30mg/sec) ie at least 17 seconds per vial. Provenzano *et al* stated that *in vitro* data suggested that ferumoxytol contained less free iron than other IV preparations and it was perhaps these physicochemical characteristics that permitted the rapid administration of larger doses compared with currently available iron preparations. The Panel considered that the statement 'The unique structure of Rienso is designed to allow rapid administration of high doses (510mg) of iron' was accurate, reflected the evidence and was capable of substantiation. The Panel thus ruled no breach of the Code.

The Panel noted its comments above and considered that its ruling of no breach of the Code in relation to describing Rienso as 'high dose' also applied to the website.

The Panel noted that one section of the website showed that to deliver 1g of iron required 2 bolus injections of Rienso and 5 bolus injections of Monofer. The Panel noted Takeda's submission that when the website was certified, Monofer injection could only be administered in maximum doses of 200mg in patients on haemodialysis but that the SPC had since been amended to allow a maximum dose of 500mg in patients on haemodialysis. The updated Monofer SPC was uploaded onto the eMC on 17 July 2013, 13 days before the complaint was submitted. Takeda had missed the update as it only monitored the eMC once a month; the company had acknowledged that the website had thus included outdated information about Monofer for some days. The material at issue could not be substantiated. Breaches of the Code were ruled.

The Panel noted the website stated that 'As with all IV irons, the use of Rienso is contraindicated in cases of: hypersensitivity to Rienso, its excipients or other iron preparations'; the complainant alleged that this was only true for Rienso. The Panel noted following a comparison of its competitors' SPCs, Rienso appeared to be the only one with hypersensitivity to other iron preparations listed as an explicit contraindication. The Panel considered that the claim thus did not reflect the available evidence and was not capable of substantiation. Breaches of the Code were ruled.

The Panel noted the allegation that the cost effectiveness section of the website only took into account the cost of the medicine and not the true cost to administer and was therefore misleading and an unfair comparison. The Panel noted Takeda's submission that while cost effectiveness was used to indicate the section of the website where cost was presented, Takeda had only claimed that Rienso was a cost-competitive option for rapid and convenient IV iron management. In the Panel's view, use of the heading 'cost effectiveness' to describe a section of the website which only detailed acquisition cost was misleading. The table

of data provided listed the 'Calculated NHS list price to administer 1g of IV iron' and thus it would be clear to the reader that the costs of the five medicines cited were acquisition costs only and did not take into account any related administration costs. Nonetheless, the Panel considered that to put such data under a heading of 'cost effectiveness' was misleading and breaches of the Code were ruled.

The Panel noted the allegation that the convenience of Rienso was debatable. It further noted Takeda's submission that Rienso offered a convenient option to patients as well as health professionals as it allowed 1g of iron to be administered with two injections in a short course, high dose, rapid bolus injection administered in 17 seconds with 30 minutes of post-dose observation over two to eight days. On balance the Panel considered that in light of current IV iron therapy, the claim that Rienso was convenient was not misleading. In that regard, the Panel ruled no breach of the Code.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of the Code was ruled. The Panel did not consider, however, that the material at issue was such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

An anonymous, non-contactable complainant complained about a Rienso (ferumoxytol) advertisement (ref April 2013 UK/RIE/1304/0040) issued by Takeda UK Ltd published in the Journal of Renal Nursing, 4 July 2013 and the website (www.anaemiazone.co.uk) (ref FE120916) referred to within it. Rienso was indicated for the intravenous (IV) treatment of iron deficiency anaemia in adults with chronic kidney disease (CKD). Patients were treated with one or two IV doses of 510mg depending on their pre-treatment haemoglobin level and body weight. Rienso particles consisted of a bioactive iron oxide core protected by a polyglucose sorbitol-carboxymethylether (PSC) coating.

A JOURNAL ADVERTISEMENT

COMPLAINT

The complainant noted that the advertisement described Rienso as 'high dose' but did not state what this was in comparison to. The complainant stated that he/she had been informed that Monofer (iron (III) isomaltoside 1000) could be given at doses of 500mg in haemodialysis patients, and 20mg/kg otherwise and in that context Rienso appeared to be low dose.

When writing to Takeda, the Authority asked it to respond in relation to Clause 7.2.

RESPONSE

Takeda noted that the complainant asked for consideration of the term 'high dose' and queried what it was being compared to. With specific reference to Clause 7.2, the complainant appeared

to be describing the term as a hanging comparison. Takeda submitted that according to the Code such comparisons whereby a medicine was described as being better or stronger or suchlike without stating that with which it was being compared were hanging comparisons and were not allowed. Takeda did not consider that the term 'high dose' compared Rienso to other medicines and submitted that it described one of Rienso's attributes. 'High dose' was presented in the advertisement on the middle of three lines of the same font size and colour indicating that the three lines were to be read in conjunction with each other as one statement thus describing Rienso as a 'Short course, High dose, Rapid bolus injection'. This summary statement described the attributes of Rienso's administration and was not inconsistent with the summary of product characteristics (SPC). Takeda submitted that its decision to describe Rienso as high dose was supported by the literature. High dose differentiated from low dose iron, as discussed by Kshirsagar *et al* (2013) which described high dose iron as doses greater than 200mg in a one month period, and low dose as ≤ 200 mg/month. Further, Schroder *et al* (2004) evaluated the use of iron sucrose and explored the safety and tolerability of 'high dose iron sucrose', with doses '7mg/kg but not exceeding 500mg'. Hence Rienso could be described as a high dose iron, as 510mg of iron was administered with each dose. Takeda denied a breach of Clause 7.2.

Takeda noted the complainant's statement that Monofer could be given at doses of 500mg in haemodialysis patients, and 20mg/kg otherwise and that in that context Rienso appeared to be low dose. Takeda submitted that as clarified above, iron doses around 500mg were described in the literature as 'high dose' and it was within that context that Takeda had described Rienso as 'high dose' and not in the context described by the complainant whose view was inconsistent with the literature.

Takeda further submitted that, as discussed above, the term 'high dose' within the advertisement was intended to be read in the context of 'Short course, High dose, Rapid bolus injection'. Rienso was only administered as a bolus injection and administration via an infusion was not described in the SPC. Conversely, Monofer offered a 20mg/kg infusion. A comparison between Rienso and Monofer's 20mg/kg infusion dose would not be appropriate, and this comparison was not made in the advertisement. Takeda denied a breach of Clause 7.2.

PANEL RULING

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

The Panel noted the complainant's submission that the advertisement described Rienso as 'high dose' but did not state what this was compared to. Takeda submitted that 'high dose' was used in

conjunction with 'Short course' and 'Rapid bolus injection' to describe the attributes of Rienso's administration and was not used to compare Rienso to other medicines. The Panel did not consider that the use of 'high dose' in this context was a hanging comparison. No breach of Clause 7.2 was ruled.

The Panel noted the complainant's further allegation that Rienso appeared to be low dose in the context of Monofer which could be given at doses of 500mg in haemodialysis patients and 20mg/kg otherwise. The Panel noted that literature provided by Takeda described high dose iron as doses greater than 200mg in a one month period. In the Panel's view the description of Rienso as high dose was supported by the literature. The Panel ruled no breach of Clause 7.2 in that regard.

B WEBSITE

COMPLAINT

The complainant noted that on the www.anaemiazone.co.uk website Rienso was described as a new IV iron whereas it had been available for over a year. The site stated that both the structure was designed to allow rapid administration of high doses. The complainant alleged that this was unlikely because Rienso appeared to cause more side effects than other IV irons especially immunological reactions and that the high dose was also incorrect. Section 3 stated that Monofer took five injections for 1g whereas it only took two. Section 3 further stated that all IV irons were contraindicated in hypersensitivity to Rienso or other iron preparations. The complainant alleged that this was only true for Rienso. The complainant further alleged that the cost effectiveness section only took into account the cost of the medicine and not the administration cost and was therefore misleading and unfair. The 'Why Rienso?' section repeated that Rienso was new which was incorrect. The complainant alleged that the claim that Rienso was convenient was very debatable in non haemodialysis patients as three other preparations only required one infusion. Finally, the cost-competitive statement was repeated although only the medicine cost was referred to. The complainant asked that the Authority look into the matter as there were several things that were of concern. The complainant submitted that he/she did not have the time to review the references in detail but considered that a more detailed review should be undertaken as there were so many issues identified upon a superficial review.

When writing to Takeda, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.3, 7.4, 7.9, 7.11 and 9.1.

RESPONSE

Takeda noted that Clause 7.11 stated that new must not be used to describe any product or presentation which had been generally available, or any therapeutic indication which had been generally promoted, for more than 12 months in the UK. The Rienso SPC stated that the date of first authorization was 15 June 2012. Takeda submitted that Rienso

was not generally available in the UK until the end of October 2012. In that regard Takeda provided a copy of a warehouse delivery note dated 25 October 2012 which detailed the shipment of quantities of Rienso. Takeda denied a breach of Clause 7.11.

In response to a request for further information on this point Takeda submitted that several months elapsed between the marketing authorization being granted for Rienso (15 June 2012) and Rienso being generally available following delivery to the UK wholesaler (October 2012). Takeda detailed the activities undertaken in chronological order. On 15 June 2012 Takeda gained marketing authorization for Rienso. On 23 July 2012 Takeda entered into an agreement with a named agency to manage the entry of Rienso into the UK NHS market. Relevant pages of the agreement were provided including one which detailed the scope of the agreement which was to map the relevant budget holders for budget impact modelling and to articulate Rienso's value proposition. Takeda's records showed that on 8 August 2012 product and therapy area training of the agency employees under the agreement of 23 July 2012 was completed. Takeda submitted that therefore the earliest that Rienso would have been promoted to any UK health professional would have been 9 August 2012. Copies of the training agenda and the corresponding certificate were provided. The full agreement with the agency was withheld. In October 2012 Rienso was delivered to the UK wholesaler and the full launch of Rienso was announced in an advertisement on 9 November 2012. The advertisement was certified on 6 November 2012 and a Rienso launch letter, certified on 13 September 2012, was distributed to health professionals on 9 November 2012.

In response to a request for further information on this point Takeda submitted that the website containing the word new had been taken down on 1 August 2013.

Takeda submitted that the construction of the particular part of the complaint wherein the complainant noted that the website stated '... both the structure is designed to allow rapid administration of high doses. Since Rienso appears to cause more side effects than other IV irons seems unlikely (especially immunological reactions) and the high dose is also incorrect' was not written clearly and appeared flawed in its editing. Takeda, however, understood the complaint to challenge Rienso's safety profile stating that there were more side effects than other IV irons. Takeda referred to its response on 'high dose' iron in Point A above.

Takeda was disappointed not to be able to ask the complainant to clarify what he/she meant by 'this seems unlikely'. Takeda would have preferred to ask what this opinion was based on so that it could adequately address the specific concern.

The complainant focused on three aspects of Rienso's safety profile: a comparison of Rienso with other IV irons; immunological reactions and concerns relating to rapid administration.

Takeda was not clear what data the complainant had

used with regard to the concern about a comparison of the safety profile of Rienso 'with other IV irons' as this concern was not consistent with its knowledge of Rienso. Takeda stated that in its view, clear comparisons of medicines could only be made from randomised head-to-head studies.

Following three phase III studies which compared Rienso with oral iron, (Spinowitz *et al* 2007, Spinowitz *et al* 2008 and Provenzano *et al* 2009) and a fourth study which focussed on safety vs placebo, (Singh *et al* 2008), a phase II safety study was undertaken to evaluate Rienso head-to-head with IV iron sucrose (Macdougall *et al* 2011). Data from this head-to-head study had been presented in a poster at the American Society of Nephrology's Kidney Week, 2011, and in a corresponding abstract. To put the results into context, one gram of IV iron was administered in the iron sucrose group (five 200mg injections if the patient was not on haemodialysis, and ten 100mg injections if the patient was on haemodialysis). In the case of Rienso, two 510mg injections were administered to all patients whether they were on haemodialysis or not. This meant, overall, patients in the iron sucrose group received five or ten exposures to iron administration, whereas in the Rienso group, patients were only exposed to two administrations of iron. The difference in the number of injections probably led to the numerical difference seen in adverse events between the two groups, as commented upon by the authors.

The iron sucrose group recorded 161 adverse events (AEs) in 53 (65%) of patients whereas 86 adverse events were experienced in 38 (48%) of patients in the Rienso group as summarised below:

AE category	Rienso (ferumoxytol) (n=80)			Iron Sucrose (n=82)		
	Events	Patients [n (%)]	Events per patient	Events	Patients [n (%)]	Events per patient
All AEs	86	38 (48)	2.3	161	53 (65)	3.0
Related AEs	8	8 (10)	1.0	46	13 (16)	3.5
SAEs	8	7 (9)	1.1	11	6 (7)	1.8
Related SAEs	1	1 (1)	1.0	1	1 (1)	1.0
AEs of special interest*	1	1 (1)	1.0	4	2 (2)	2.0
AEs leading to drug discontinuation	1	1 (1)	1.0	7	4 (5)	1.3

*acute moderate-to-severe acute hypotension and hypersensitivity reactions

Takeda submitted that it was clear the complainant's statement 'more side effects than other IV irons' was not substantiated by this head-to-head study. With regard to the safety study, alluded to earlier (Singh *et al*), the authors concluded that ferumoxytol was 'well tolerated and had a safety profile similar to placebo in anaemic patients with CKD stage 1 to 5D', (ie patients with mild CKD through to end-stage renal disease who required treatment with haemodialysis). This was not in breach of Clause 7.9.

Takeda submitted that from the data presented, immunological reactions were captured as AEs of special interest and the results with Rienso were similar to iron sucrose.

Section 4.8 of the Rienso SPC stated that in clinical trials involving 1,562 subjects, serious hypersensitivity or hypotensive reactions were uncommon, and were reported in 3 (0.2%) of patients. One of these three cases was characterised as an anaphylactoid reaction. Also, the system organ class, immune system disorders, had hypersensitivity including anaphylaxis classified as uncommon, and life-threatening anaphylactic/anaphylactoid reactions with a frequency that was not estimable from the available data.

The concern over the anaphylactic/anaphylactoid reactions with all IV irons had been flagged to the European Medicines Agency (EMA) by the French regulatory authority and the entire class had come under scrutiny via Article 31 of the EU Directive 2001/83/EC. This had now concluded and a report was published on 28 June 2013. In particular, for the point discussed here, all IV irons had a small risk of causing allergic reactions which could be life-threatening if not treated promptly. The recommendations also included that patients should be closely observed for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following each injection of an IV iron. This was a blanket opinion on the class of IV irons, and a distinction was not drawn between the available preparations. Takeda awaited the decision of the European Commission as to whether to make the Committee for Medicinal Products for Human Use (CHMP) recommendations legally binding across the European Union, and to learn how this might affect every respective iron SPC.

Takeda submitted that all information on the website about side effects reflected the available evidence and therefore was not in breach of Clause 7.9.

The Rienso SPC also included data from a post-marketing observational study which retrospectively analysed data from over 8,600 patients who had attended three large dialysis clinics in the US. This showed that, over a 1 year period, more than 33,300 doses of Rienso were administered. Almost 50% of patients received repeat dosing with 4 or more doses. Mean haemoglobin increased by 0.5-0.9 g/dL post-treatment and stabilised in the range of 11-11.7g/dL over the 10 month post-dose period; no new safety signals were identified with repeat dosing.

Takeda noted that Clause 7.9 stated that information and claims about side effects should be capable of substantiation by clinical experience. With the information described above from the post-marketing observational study, Takeda submitted that clinical experience substantiated the information on the website regarding side effects and therefore Takeda denied a breach of Clause 7.9.

Takeda noted the complainant's concern regarding

the safety of administering Rienso as a rapid bolus injection. Provenzano *et al*, in a phase III trial which compared Rienso with oral iron, explained that the body of evidence demonstrated that Rienso had an acceptable pharmacokinetic profile that allowed bolus dosing, which included lower free iron saturations than comparator irons, such as a 6-fold lower catalytically active iron concentration (bleomycin detectable free iron) than iron sucrose, Jacobs *et al* (2004) (abstract). Jahn *et al* (2011) also demonstrated low free iron concentration with Rienso.

The above information illustrated that there were no concerns about Rienso being administered as a rapid bolus injection. Also, it was true to state that within the class of IV iron administration, when comparing products' SPCs, Rienso was indeed rapid as a 510mg dose could be administered in a minimum of 17 seconds, making it the quickest iron available to administer such a quantity in its class.

With reference to rapid administration of iron, Takeda submitted that it had not misled the reader as the information provided was accurate, balanced, fair, objective and unambiguous based upon contemporaneous data which clearly reflected all of the evidence available. Additionally the claim of rapid bolus injection was not inconsistent with the Rienso SPC.

Takeda submitted that when the website was certified, Monofer could only be administered in maximum doses of 200mg in patients on haemodialysis. The Monofer SPC had since been amended to allow a maximum of 500mg in haemodialysis patients. The updated SPC was uploaded onto the electronic Medicines Compendium (eMC) on 17 July, thirteen days before the complaint.

Takeda submitted that in addition to daily monitoring of the media and scientific journal scanning services, it adhered to a policy which required manual checking of the eMC monthly to monitor competitors' SPCs. Takeda submitted that this was an appropriate interval. As there had been no press coverage about the change to the Monofer SPC, Takeda had not noticed the change to the competitors' SPC in the relatively short time it took the complainant to write his/her letter as a maximum of one month had not elapsed since the SPC was updated on the eMC website.

Takeda submitted that it did not intend to mislead health professionals, whilst it acknowledged that absence of awareness was not a justification, Takeda noted that its action of immediately withdrawing the website upon hearing its competitors' news demonstrated its commitment to the spirit of the Code. Takeda submitted that since receiving this complaint, it would check eMC twice-weekly until it received advice from the Panel on the appropriate interval for competitor surveillance. Takeda submitted that it had also withdrawn all other materials that referred to Monofer having a 200mg cap for administration in haemodialysis. Takeda considered that, despite reasonable competitor

monitoring and its intention to provide factually accurate, up-to-date information without misleading the reader, the website might technically be in breach of Clause 7.2.

Takeda submitted that it had explored its competitors' SPCs regarding warnings and precautions and contraindications when investigating the complainant's allegation that whilst the website stated that all IV irons were contraindicated in hypersensitivity to Rienso or other iron preparations, this was only true for Rienso. Takeda noted that patient safety was of particular concern for industry and health professionals especially since every IV iron contained warnings regarding hypersensitivity or anaphylaxis/anaphylactoid reactions. Takeda listed the contraindications relating to hypersensitivity to iron for each brand's active substance.

Brand	Active substance	Contraindications
Rienso	Iron – as ferumoxytol	1 Hypersensitivity to the active substance or to any of the excipients 2 Hypersensitivity to other iron preparations
Venofer	Iron – as iron sucrose	1 Known hypersensitivity to Venofer or any of its excipients
Ferinject	Iron – as ferric carboxymaltose	1 Known hypersensitivity to Ferinject or any of its excipients
Cosmofer	Iron (III) – as iron (III) -hydroxide dextran complex	1 Drug hypersensitivity including iron mono-or disaccharide complexes and dextran
Monofer	Iron – as iron (III) isomaltoside	1 Hypersensitivity to the active substance or to any of the excipients

Rienso appeared to be the 'odd one out' where 'hypersensitivity to other iron preparations' was an explicit contraindication. Cosmofer included a contraindication to drug hypersensitivity including iron mono- or disaccharide complexes and dextran, some of which were in effect other iron preparations and therefore Rienso was not the only one with such a contraindication.

Takeda noted that Rienso was the only IV iron that had been granted a marketing authorization via the centralised procedure with the EMA which might indicate why it had the additional contraindication of hypersensitivity to other iron preparations.

When the website was in development, Takeda's view was that iron was iron regardless of the brand administered. Takeda appreciated that excipients differed between brands but noted that iron was the active ingredient for each preparation and assumed

that its competitors' respective contraindications relating to hypersensitivity to iron, either described as the brand name or as an active substance meant that hypersensitivity to any iron preparation was in principle a contraindication for every brand. The recently published CHMP recommendations on how to manage the risk of allergic reactions with IV iron-containing medicines concluded that provided adequate measures to reduce the risk of allergic reactions were taken, this class of medicine had benefits that outweighed the risks. Caution was warranted with every dose of IV iron, even if previous administrations had been well tolerated. The CHMP opinion stated that 'intravenous iron-containing products were contraindicated in patients with hypersensitivity to the active substance or excipients, and intravenous iron-containing products must not be used in patients with serious hypersensitivity to other parenteral iron products'. Takeda submitted that the body of evidence appeared to point in the direction that all IV iron preparations should carry a contraindication of hypersensitivity to other IV iron preparations which was in line with its interpretation when it developed the website. The therapy area awaited the decision of the European Commission as to how the CHMP opinion should be reflected in the class's SPCs.

Takeda submitted that the statement on its website reflected the general belief about the use of IV irons after hypersensitivity had already been experienced to one IV iron preparation as supported by the CHMP report on this matter. Takeda denied a breach of Clause 7.4.

With regard to the complainant's allegation that the section entitled 'cost-effectiveness' only took into account the cost of the medicine and not the true cost to administer which was misleading and unfair, Takeda noted that it claimed that Rienso was a cost-competitive option for rapid and convenient IV iron management in CKD and substantiated it by tabulating prices. In descending order of price, compared with Ferinject and Monofer, Rienso was cheaper. Takeda noted that it could clearly not claim that Rienso was the cheapest option as Cosmofer and Venofer were cheaper and so it used 'cost-competitive'. The voiceover did not make any additional claim. Takeda noted that the complaint was based on a discussion of the meaning of 'cost'. The www.thefreedictionary.com defined cost as, *inter alia*, 'an amount paid or required in payment for a purchase; a price'. Cost was therefore synonymous with price. The term 'cost-effectiveness' was used to indicate the section of the website where cost was presented. It was named in a similar fashion to Section 2, where 'safety' indicated where the safety data was presented without necessarily making the claim that 'Rienso was safe' as this was not allowed. Takeda denied that its claim of cost-competitiveness was misleading, and was not an unfair comparison as alleged.

Takeda noted that the complainant had been led to the website from a journal advertisement which included the claim 'new SMC [Scottish Medicines Consortium] advice available' which referred to SMC's website where a cost minimisation analysis was discussed which led to the publication of the

SMC's advice for NHS Scotland. Takeda decided not to place the SMC advice on the website as this important information for Rienso was presented in other promotional materials that subsequently directed health professionals to the SMC website and to www.anaemiazone.co.uk. The Takeda UK website had not undergone search engine optimisation and did not appear early in the hit list when searching for Rienso. It was unlikely that the website would be read in isolation. Takeda denied breaches of Clauses 7.2, 7.3 and 7.4.

Takeda agreed that debate was needed regarding the complainant's view that the convenience Rienso offered was 'very debatable in non haemodialysis patients as three other preparations only require one infusion'. Takeda submitted that Rienso was convenient to administer because 1g of iron could be administered with two injections in a short course, high dose, rapid bolus injection over two to eight days. Takeda noted that the complainant appeared to consider that an infusion over a number of hours with the additional expenditure of nurse time and the use of NHS services and the ensuing observation period was more convenient than the administration of one or two rapid bolus injections which were each administered in as little as 17 seconds, with 30 minutes of post-dose observation, over two visits (if a second dose was needed) within two to eight days. Takeda disagreed with the complainant's opinion. There were pros and cons for each side of the argument but Takeda submitted that Rienso offered a convenient option for patients and health professionals. Takeda denied a breach of the Code.

In summary, Takeda was disappointed that despite the website offering contact details and a medical information option, the complainant approached the PMCPA. Takeda submitted that despite monitoring the eMC website at monthly intervals, which demonstrated its intention to uphold the spirit of Clause 7.2, it had technically breached the Code with respect to a competitor's SPC. Takeda noted that the complainant appeared to be very well acquainted with the competitor's SPC and its update as the complaint was written within 13 days of the update appearing on the eMC. Takeda denied a breach of Clauses 7.3, 7.4, 7.9 and 7.11 with regards to the website.

Takeda submitted that although it did not notice an unannounced update to a competitor's SPC despite regular surveillance, it did not consider that it had failed to maintain high standards and denied a breach of Clause 9.1. Subsequently Takeda denied a breach of Clause 2 which was reserved for circumstances where activities or materials associated with promotion had brought discredit to, and reduced of confidence in, the industry.

Takeda maintained its strong commitment to adhere to the letter and spirit of the Code and its value of the importance of the industry's position in the wider society.

PANEL RULING

The Panel noted, with regard to the allegation that

Rienso was described on the website as a new IV iron whereas it had been available for over a year, that the Rienso SPC listed 15 June 2012 as the date of first authorization. The Panel further noted Takeda's account of its activities subsequent to that date and its submission that Rienso could not have been promoted to any UK health professional before 8 August 2012 as this was when the training of the agency's employees was completed. The Panel noted, however, that the contract between the agency and Takeda stated that '[the agency] would carry out and perform the services...' with effect from the commencement date....' ie from 23 July. The Panel noted that the services included navigating the changing NHS in the correct timelines with the correct information (advanced product notification (APN) and budget impact model) to ensure appropriate local product update. Reference was made to engaging the right decision makers in a local health economy who planned the budget and introduction of new oncology medicines and ensure key opinion leader advocacy at launch. The advanced product notification referred to budgetary conversations that would take place with relevant NHS budget holders. The Panel noted that these activities would be carried out from 23 July ie 5-6 weeks after Rienso had received its marketing authorization. The Panel considered that such activity with Rienso was promotional. In that regard Rienso had thus been promoted since 23 July 2012 and so, to meet the requirements of the Code, could not be described as 'new' beyond 22 July 2013. The Panel noted Takeda's submission, however, that the product had been described as new on the anaemiazone.co.uk website until 1 August 2013. A breach of Clause 7.11 was ruled.

The Panel noted the complainant's view that the site stated the structure was designed to allow rapid administration of high dose but that seemed unlikely since Rienso appeared to cause more side effects than other IV irons (especially immunological reactions). The Panel understood the complainant to mean that as Rienso caused more side effects than other IV irons (especially immunological reactions) it was unlikely that the structure was designed to allow rapid administration of a high dose. The complainant did not provide any evidence to support his/her allegation. The Panel noted that the website stated that 'The unique structure of Rienso is designed to allow rapid administration of high doses (510mg) of iron'. A bullet point below stated that the protective PSC coating shielded the bioactive iron oxide from the plasma to reduce immunological sensitivity and reduce release of free iron. The Panel noted that Section 4.8 of the Rienso SPC stated that in clinical trials involving 1,562 subjects, serious hypersensitivity or hypotensive reactions were uncommon, and were reported in 3 (0.2%) of patients with CKD who received Rienso. The Panel further noted that all of the IV iron SPCs provided by Takeda stated that parenteral administration of all iron complexes might cause immediate severe and potentially lethal hypersensitivity reactions. In the Panel's view no evidence was provided to support the allegation that Rienso caused more side effects than other IV irons (especially immunological reactions). The Panel noted that

according to the SPC, Rienso was administered as an undiluted IV injection delivered at a rate of up to 1ml/sec (30mg/sec) ie at least 17 seconds per vial. Provenzano *et al* stated that in vitro data suggested that ferumoxytol contained less free iron than other IV preparations and it was perhaps these physicochemical characteristics that permitted the rapid administration of larger doses of ferumoxytol compared with currently available iron preparations. The Panel considered that the statement 'The unique structure of Rienso is designed to allow rapid administration of high doses (510mg) of iron' was accurate, reflected the evidence and was capable of substantiation. The Panel thus ruled no breach of Clauses 7.2 and 7.4.

The Panel noted its comments at Point A above and considered that its ruling of no breach of Clause 7.2 in relation to describing Rienso as 'high dose' also applied to the website.

The Panel noted that Section 1 of the website (not 3 as referred to by the complainant) contained a bar chart headed 'FEWER bolus injections to deliver 1g iron vs most other IV irons' which showed that to deliver 1g of iron required 2 bolus injections of Rienso and 5 bolus injections of Monofer. The Panel noted Takeda's submission that when the website was certified, Monofer injection could only be administered in maximum doses of 200mg in patients on haemodialysis but that the SPC had since been amended to allow a maximum dose of 500mg in patients on haemodialysis. The updated Monofer SPC was uploaded onto the eMC on 17 July 2013, 13 days before the complaint was submitted. Takeda had missed the update as it only monitored the eMC once a month; the company had acknowledged that the website at issue had thus included outdated information about Monofer for some days. Clause 7.2 of the Code required information and claims to be up-to-date and in that regard there was no grace period. The Panel ruled a breach of Clause 7.2. The material at issue could not be substantiated. The Panel ruled a breach of Clause 7.4.

The Panel noted the website stated that 'As with all IV irons, the use of Rienso is contraindicated in cases of: hypersensitivity to Rienso, its excipients or other iron preparations'; the complainant alleged that this was only true for Rienso. The Panel noted Takeda's acknowledgement that, following a comparison of its competitors' SPCs, Rienso appeared to be the only one with hypersensitivity to other iron preparations listed as an explicit contraindication. The Panel considered that the claim thus did not reflect the available evidence and was not capable of

substantiation. A breach of Clauses 7.4 and 7.9 was ruled.

The Panel noted the allegation that the cost effectiveness section of the website (Section 4) only took into account the cost of the medicine and not the true cost to administer and was therefore misleading and an unfair comparison. The Panel noted Takeda's submission that while cost effectiveness was used to indicate the section of the website where cost was presented, Takeda had only claimed that Rienso was a cost-competitive option for rapid and convenient IV iron management. In the Panel's view, use of the heading 'cost effectiveness' to describe a section of the website which only detailed acquisition cost was misleading. The table of data provided in Section 4 of the website listed the 'Calculated NHS list price to administer 1g of IV iron' and thus it would be clear to the reader that the costs of the five medicines cited were acquisition costs only and did not take into account any related administration costs. Nonetheless, the Panel considered that to put such data under a heading of 'cost effectiveness' was misleading and a breach of Clauses 7.2 and 7.3 was ruled.

With regard to the allegation that the claim that Rienso was a convenient way to deliver 1g of iron was very debatable in non haemodialysis patients, as three other preparations only required one infusion, the Panel noted Takeda's submission that Rienso offered a convenient option to patients as well as health professionals as it allowed 1g of iron to be administered with two injections in a short course, high dose, rapid bolus injection administered in 17 seconds with 30 minutes of post-dose observation over two to eight days. On balance the Panel considered that in light of current IV iron therapy, the claim that Rienso was convenient was not misleading. In that regard, the Panel ruled no breach of Clause 7.2.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider, however, that the material at issue was such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

Complaint received	30 July 2013
Case completed	11 October 2013

ANONYMOUS v SANOFI

Conduct of representative

An anonymous, non-contactable complainant criticised the conduct of a named Sanofi medical representative.

The complainant alleged that the named representative had visited a local hospital on a number of occasions and behaved rudely. The complainant stated that on his latest visit (25 July 2013), the representative had sworn a number of times in front of staff and patients. The complainant alleged that the representative's aggression was unacceptable.

The detailed response from Sanofi is given below.

The Panel noted that extreme dissatisfaction was usually required on the part of an individual before he or she was moved to complain. The Panel noted Sanofi's submission that the representative in question had not worked at Sanofi since March 2013 and it could find nothing related to the representative's behaviours, either with customers or within the team in which he/she worked, which was a cause for concern during his time at Sanofi. The Panel further noted Sanofi's submission that there was no record of any Sanofi representative attending the hospital in question on 25 July.

The Panel noted that the complainant was anonymous and non contactable and could therefore not be asked for more information. A complainant had the burden of proving his/her complaint on the balance of probabilities. The complainant had not provided any material to support his/her allegations. The Panel noted that it was extremely difficult in such cases to know exactly what had transpired. The representative in question no longer worked for Sanofi. A judgement had to be made on the available evidence and on the balance of probabilities. The Panel did not consider that the complainant had established that the representative in question had behaved as alleged and therefore failed to maintain a high standard of ethical conduct. No breaches of the Code were ruled, including no breach of Clause 2.

An anonymous, non-contactable complainant criticised the conduct of a named Sanofi medical representative.

COMPLAINT

The complainant alleged that the named representative had visited a local hospital on a number of occasions and behaved rudely. The complainant stated that on his latest visit (25 July 2013), the representative had sworn a number of times in front of staff and patients. The complainant was very proud of the hospital and alleged that the representative's aggression was unacceptable. The

complainant stated that he/she had submitted this complaint on the advice of a local cardiologist.

When writing to Sanofi, the Authority asked it to respond in relation to Clauses 2, 9.1 and 15.2 of the Code.

RESPONSE

Sanofi stated that no-one of the name referred to by the complainant worked for the company in the UK. There had previously been a representative of a similar name (but slightly different spelling) but he had not been employed by Sanofi since March 2013. Sanofi stated that it was thus unable to provide any information in relation to the representative's alleged visit on 25 July 2013.

In response to a request for further information from the case preparation manager, Sanofi noted that the complainant had also commented on the individual's rude manner 'on a number of occasions'. With this in mind, Sanofi submitted that it had asked the representative's previous line manager to provide evidence of the representative's behaviours at various field visits over the last year at Sanofi. Sanofi confirmed that the representative's role (as a representative of its cardiology division) included visits to the hospital in question; Sanofi provided a copy of the various field visit reports as requested, along with a statement from the manager on his overall assessment of the representative. Sanofi noted that at his end-of-year appraisal assessment in December 2012, the representative achieved all of his priorities (objectives) and demonstrated the appropriate level of expected competencies (behaviours). The representative had passed the ABPI Representatives Examination.

Sanofi stated that it had assessed the collected evidence and could find nothing related to the representative's behaviours, either with customers or within the team in which he worked, which was a cause for concern during his time at Sanofi.

Sanofi therefore denied any breach of the Code.

In response to a request for further information from the Panel, Sanofi submitted that it had checked its sales team call recording database and could find no record of any Sanofi representative attending the hospital in question on 25 July 2013.

PANEL RULING

The Panel noted that extreme dissatisfaction was usually required on the part of an individual before he or she was moved to complain. The Panel noted Sanofi's submission that the representative in question had not worked at Sanofi since March

2013 and it could find nothing related to the representative's behaviours, either with customers or within the team in which he/she worked, which was a cause for concern during his time at Sanofi. The Panel further noted Sanofi's submission that there was no record of any Sanofi representative attending the hospital in question on 25 July.

The Panel noted that the complainant was anonymous and non contactable and could therefore not be contacted for more information. A complainant had the burden of proving his/her complaint on the balance of probabilities. The complainant had not provided any material to support his/her allegations. The Panel noted that it was extremely difficult in such cases to know exactly

what had transpired. The representative in question no longer worked for Sanofi. A judgement had to be made on the available evidence and on the balance of probabilities. The Panel did not consider that the complainant had established that the representative in question had behaved as alleged and therefore failed to maintain a high standard of ethical conduct. No breach of Clause 15.2 was ruled. The Panel also ruled no breach of Clauses 9.1 and 2.

Complaint received

2 August 2013

Case completed

9 September 2013

VOLUNTARY ADMISSION BY OTSUKA

Representatives' briefing material

Otsuka Pharmaceuticals voluntarily admitted that a regional business manager (RBM) had briefed his/her sales team such that he/she appeared to set a call frequency target which would lead to a breach of the Code.

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

Otsuka submitted that following a team teleconference in late October 2012, the RBM in question emailed the team with the following:

'The focus is on next fortnight till end of October should consist of as follows:

1. List of target customers who have already been seen on a frequency of 2 – 4 times and need to move them to 8 – 9 calls. Please put in your plans when you plan to see them this month.
2. Who you plan to follow up after your meetings (1st call within 48 hours and followed by a second call in 10 days)'.

In Otsuka's view, 'calls' used in this context implied proactivity. The call frequency stipulated exceeded that which had been agreed in the performance appraisal document and exceeded those that were acceptable under the Code (maximum 3 unsolicited calls per year). Otsuka stated that the email specified plans for customers seen 'less than 3 times' and plans to achieve this target and plans for a single follow-up post-meeting, both of which were within the Code. Otsuka understood that the RBM might have used the word 'call' in error instead of 'contact'. However, even if this was so, stipulating the requirement for increased activity to potentially require 6-7 contacts with individual customers in a 3-month period remained excessive, as was 2 contacts within a 10-day period.

Otsuka submitted that the RBM's instruction was in breach of the Code. All field employees underwent training. It was unclear if this instruction translated to actual non-compliant activity by the representatives, but the assumption had to be that it had.

The detailed response from Otsuka is given below.

The Panel noted that the email sent to two sales teams stated that the focus of the next fortnight until the end of the month should consist of; list of target customers who had already been seen 2-4 times and move them to 8-9 calls. In the Panel's view 'calls' implied unsolicited 1:1 meetings with a doctor or other health professional which, as noted

above, should not normally exceed three on average each year. The RBM stated in the email 'Please put in your plans when you plan to see them this month'. The Panel considered that the email implied that, having already called upon a customer 2-4 times, representatives should arrange to see them a further 4 to 7 times within a fortnight. The email also referred to a follow up call within 48 hours following their meetings, followed by a second call in 10 days.

The Panel considered that the RBM's email advocated a course of action which would not comply with the requirements of the Code. The Panel noted Otsuka's submission that it was unclear if the email had translated into non-compliant activity by the sales force but the assumption had to be that it had and on that basis the Panel ruled a breach of the Code as acknowledged by Otsuka.

The Panel further noted that the Code required representatives' briefing material to be certified. In so much as the email instructed representatives about how many times they should see customers to promote a named medicine, the Panel considered that the email should have been certified which it had not been. A breach of the Code was ruled as acknowledged by Otsuka.

Otsuka Pharmaceuticals (UK) Limited voluntarily admitted that a regional business manager (RBM) had briefed his/her sales team such that he/she appeared to set a call frequency target which would lead to a breach of the Code.

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

COMPLAINT

Otsuka noted that Clause 15.4 of the Code referred to the frequency and manner of calls on doctors and others prescribers. The company's annual objectives template for sales representatives contained metrics by which their activities were measured. Specific metrics related to individual territories based on geographical size and customer base. However, the over-arching specification for the objectives was that they had to adhere to the Code as follows:

'All activity objectives must be met only by following [in-house standard operating procedures (SOPs)] and in compliance with ABPI Code of Practice guidance (particularly Clause 15.4). Reference to "calls" in these objectives means 1:1 activity, which in addition to unsolicited calls will include those prearranged, or requested by a doctor or other prescriber, or calls made in order to respond to a specific

enquiry. Reference to “contacts” means all “calls” outlined above plus attendance at group meetings and visits to follow up on a report of an adverse reaction.’

Otsuka submitted that following a team teleconference in late October 2012, the RBM in question emailed the team with the following:

‘The focus is on next fortnight till end of October should consist of as follows:

1. List of target customers who have already been seen on a frequency of 2 – 4 times and need to move them to 8 – 9 calls. Please put in your plans when you plan to see them this month.
2. Who you plan to follow up after your meetings (1st call within 48 hours and followed by a second call in 10 days)‘.

In Otsuka’s view, ‘calls’ used in this context implied proactivity. The call frequency stipulated exceeded that which had been agreed in the performance appraisal document and exceeded those that were acceptable under the Code (maximum 3 unsolicited calls per year). Otsuka stated that the 30-day plan included in the email specified plans for customers seen ‘less than 3 times’ and plans to achieve this target and plans for a single follow-up post-meeting, both of which were within the Code. Otsuka understood that the RBM might have used the word ‘call’ in error instead of ‘contact’. However, even if this was the case, stipulating the requirement for increased activity to potentially require 6-7 contacts with individual customers within a 3-month period remained excessive, as was 2 contacts within a 10-day period.

Otsuka submitted that the RBM’s instruction was in breach of Clause 15.4. All field employees underwent an introductory presentation by medical affairs to emphasise adherence to the Code and various SOP requirements. It was unclear if this instruction translated to actual non-compliant activity by the representatives, but the assumption had to be that it had. It had been made clear to the RBM that this type of instruction was not acceptable. Business unit managers had been instructed to brief their managers on appropriateness of emails – any instructional emails must get a second opinion on the need for certification. All managers had also been mandated to attend Code re-training which would take place shortly.

RESPONSE

Otsuka provided copies of relevant documents and also noted a possible breach of Clause 14 as neither the RBM’s email nor the 30-day plan which accompanied it were reviewed or certified as required by Otsuka’s SOP which stipulated that all briefing materials had to be entered into Zinc. In addition the 30-day plan was subsequently dropped and not implemented.

Otsuka noted that Section 6.2 of its copy approval SOP stated that all representatives’ training and briefing materials related to the promotion of a medicine had to be certified and that written communications to representatives which contained instructions which might constitute a briefing (eg emails) must be certified. Otsuka provided a copy of the RBM’s self-study training form in which he/she stated that he/she had read and understood the copy approval SOP.

Otsuka also provided a copy of the certificate and template related to a sales representative’s annual performance objectives for 2012. The overarching direction for the activities stated that all activities objectives must be met only by following Otsuka SOPs and in compliance with the Code and drew attention to Clause 15.4. It also included a definition of ‘calls’ and ‘contacts’. The certified template allowed for the individual target call rate to be customised according to the territory size and number of potential doctors within it.

Otsuka further provided a copy of the certificate and email related to its corrective and preventative actions (CAPA) following the non-compliant email which noted that briefings must be certified through Zinc.

PANEL RULING

The Panel noted that the supplementary information to Clause 15.4 stated that companies should arrange that intervals between visits did not cause inconvenience. The number of calls made on a doctor or other prescriber by a representative each year should not normally exceed three on average. This did not include: attendance at group meetings, including audio-visual presentations and the like; a visit requested by a doctor or other prescriber or a call made to respond to a specific enquiry; a visit to follow up a report of an adverse reaction. When companies briefed representatives, they should distinguish clearly between expected call rates (ie not normally more than three on average in a year) and expected contact rates (ie calls plus group meetings, visits to follow up a report of an adverse reaction etc). Targets must be realistic and not such that representatives breached the Code in order to meet them.

The Panel noted that the email sent from the RBM in October to two product sales teams stated that the focus of the next fortnight until the end of the month should consist of; list of target customers who had already been seen 2-4 times and move them to 8-9 calls. In the Panel’s view ‘calls’ implied unsolicited 1:1 meetings with a doctor or other health professional which, as noted above, should not normally exceed three on average each year. The RBM stated in the email ‘Please put in your plans when you plan to see them this month’. The Panel considered that the email implied that, having already called upon a customer 2-4 times, representatives should arrange to see them a further 4 to 7 times more within the space of a fortnight. The email also referred to a follow up call within 48

hours following their meetings, followed by a second call in 10 days.

The Panel considered that the email sent by the RBM advocated a course of action which would not comply with the requirements of Clause 15.4. The Panel noted Otsuka's submission that it was unclear if the email had translated into non-compliant activity by the sales force but the assumption had to be that it had and on that basis the Panel ruled a breach of Clause 15.4 as acknowledged by Otsuka.

The Panel further noted that the Code required representatives' briefing material to be certified. In

so much as the email instructed representatives about how many times they should see customers to promote a named medicine, the Panel considered that the email should have been certified which it had not been. A breach of Clause 14.1 was ruled as acknowledged by Otsuka.

Complaint received

2 August 2013

Case completed

3 September 2013

MEDICINES MANAGEMENT PHARMACIST v LEO

Template letter to request GP initiation of Picato

A medicines management pharmacist complained about pre-printed forms for Picato gel (ingenol mebutate) issued by Leo Pharma that could be used by dermatologists to communicate their prescribing recommendations to GPs. The complainant was concerned that the forms were being used locally to get around the fact that Picato was not on the formulary.

The detailed response from Leo is given below.

The Panel noted that the material in question was a preprinted letter addressed 'Dear Dr' which recommended that a patient be prescribed Picato. There was space for the doctor to include patient and clinical details. This was followed by details of Picato's indication and some clinical trial outcomes and provision for the clinician's signature. Prescribing information was included on the reverse.

The Panel noted that the Code did not necessarily prohibit the promotion of non-formulary medicines, but such promotion had to comply with the Code. In this regard, the Panel noted that in relation to representatives the Code stated, *inter alia*, that the arrangements in force at any particular establishment must be observed.

The Panel noted that according to Leo, Picato was on a local clinical commissioning group and trust formulary and that a review of a formulary submission to a local medicines management group had been deferred. The Panel noted Leo's submission that there were no published restrictions preventing the promotion of medicines prior to formulary inclusion in the five hospitals where the material was distributed. The relevant local medicines management group policy on certain meetings stated that ideally the medicines management group would prefer that companies promoted mainly products included in the local formulary or those that had been approved for use within the local health economy. It did not otherwise restrict or comment on the promotion of non-formulary medicines. In addition, the Panel noted Leo's submission that the referral footprint of dermatologists at the hospitals where the item was distributed included practices not covered by the guidance.

The Panel noted that the complainant was concerned that the promotional material was being distributed despite Picato's non-formulary status. The Panel noted that the material in question did not comment on or raise any inferences about Picato's formulary status. The Panel did not consider that the material gave a misleading impression about Picato's formulary status and in that regard ruled no breach of the Code.

The Panel noted its comments above on the relevant requirements of the Code and local guidelines. The Panel did not consider that the company had failed to maintain high standards in this regard. No breach of the Code was ruled.

A medicines management pharmacist at a clinical commissioning group (CCG), complained about a piece of promotional material for Picato gel (ingenol mebutate) issued by Leo Pharma which was in the form of a pad of 30 pre-printed A4 forms (ref 4340a/000526).

The form could be used as a template for dermatologists to communicate their prescribing recommendations to GPs. It was distributed to dermatologists, specialist registrars and a few GPs with a special interest in dermatology.

Picato was indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

COMPLAINT

The complainant stated that as a result of one of the forms (with prescribing information on the reverse) making its way to a surgery where she worked as a pharmacist (it was not clear whether this was via a patient), one of the GPs there asked her whether he should prescribe Picato. The complainant had looked into this matter on his behalf and was advised by the local commissioning support unit (CSU) that Picato was not presently on the formulary as the request was initiated by Leo rather than via a dermatologist as was customary. The complainant had therefore advised the GP that he should instead prescribe solaraze as this was recommended first line for actinic keratosis. The medicines management team was concerned, however, that the forms were being used across the local health economy to get around the fact that Picato was not on the formulary.

When writing to Leo Pharma, the Authority asked it to respond in relation to Clauses 7.2 and 9.1 of the Code.

RESPONSE

Leo stated that the forms, which had been certified for promotional use, were offered in face-to-face meetings to dermatologists and specialists throughout the UK and not only in those areas where Picato was not on the local formulary. Leo explained that in the area in question, the forms were distributed by two representatives to specialist secondary care dermatologists, specialist registrars and to four GPs with a special interest (GPSIs) in dermatology, from the end of February 2013 to date.

Although most of the forms were distributed in five hospitals, one in particular received more than the others. Where accepted, each dermatologist or specialist recipient received one book containing a pad of 30 forms. Leo submitted that the local representatives advised dermatologists that Picato was on a local CCG and trust formulary (from 13 April) and that a submission to the local medicines management group was due for review on 13 July (which had subsequently been deferred). The health professionals that they were distributed to had the expertise and authority to both prescribe, and recommend the prescription of, Picato according to their clinical judgement in individual patients. Leo representatives were briefed on the appropriate use of the forms before they were distributed.

Leo submitted that although the Code did not specifically preclude promotional activities prior to formulary inclusion, before distributing the forms, the local representatives took due care to find out about, and act in accordance with, local NHS restrictions on the promotion of products. There were no published restrictions preventing the promotion of medicines prior to formulary inclusion in the five hospitals where the forms were distributed including the hospital which received the majority of forms due to its status as a national tertiary referral centre and because it was the primary base for most local dermatologists.

Leo representatives were briefed that they should distribute the forms to dermatologists and GPSIs so that, if they wished, they could use it as a detailed template for communicating their prescribing recommendations clearly to the patients' GPs, some of whom would not be in the local area.

The decision to recommend Picato in a particular patient (based on their clinical need and any applicable formulary restrictions in the locality of the patient) was entirely the responsibility of the dermatologist, specialist registrar or GPSI. The representatives did not request any dermatologist to recommend Picato for patients that they knew were resident where Picato was not on the local formulary. At no point did Leo representatives ask them to prescribe Picato for any specific patient or to direct their prescribing recommendations towards patients from any particular locality. The further distribution of the template letter was at all times, in the control of the recipient specialist.

With regard to primary care (which covered GPs & GPSIs), local medicines management group in conjunction with the local CSU provided guidance to GPs on medicines use and a list of recommended (formulary) products. Until recently, the local medicines management group did not have any published local restrictions on the promotion of products prior to their inclusion on its formulary. The local medicines management group published a guidance document on its website towards the end of July and a copy was provided. Leo submitted that this guidance only restricted the promotion of non-formulary medicines at company sponsored educational meetings and not their promotion in other contexts.

Leo noted that the local medicines management group guidance allowed for the recommendation by specialists of medicines which were not on its formulary in restricted instances. The group's website page headed 'Formulary Subgroup' stated that: 'The formulary is applicable to new initiations and treatments in approximately 80% of patients'. Leo submitted that it would be the responsibility of the specialist to be aware of, and act within these restrictions when recommending a medicine to their primary care colleagues. It was also important to note that the referral 'footprint' of dermatologists at the hospitals where this item was distributed, included GP practices outside the local area which were not covered by local guidance.

Leo stated that, in summary:

- this was a promotional item which contained accurate information appropriate to the recipients;
- the representatives were briefed on the use of the forms prior to their distribution;
- the representatives made themselves aware of locally published restrictions on the promotion of medicines;
- there were no published, blanket local restrictions which prevented the promotion of non-formulary medicines;
- recipients were not requested to prescribe Picato in any specific patients nor direct their prescribing recommendations to patients from any particular locality;
- recipients were, at all times, in full control of the further distribution of the forms.

With regard to Clause 7.2, Leo submitted that the forms contained no claims or information in relation to the local or regional formulary review or inclusion status of Picato, nor was there any recommendation to prescribe Picato before inclusion in any formulary or guidelines. All the information contained in the form related purely to providing clarity to the recipient GP on what the specialist had recommended, how that clinical recommendation could be implemented and key summary information on Picato. All of this information was accurate, balanced and capable of substantiation.

Leo reiterated that the decision to recommend Picato in a particular patient (based on their clinical need and any applicable local formulary restrictions) was entirely the responsibility of the dermatologist. Leo representatives did not ask dermatologists to prescribe Picato for any specific patient or direct their prescribing recommendations towards patients from any particular locality, nor were specialists asked to distribute the forms to localities where Picato was not on formulary.

Leo stated that it was common practice for many hospital consultants to advise and recommend prescription of medicines by GPs for their referred patients rather than provide a hospital prescription. This was dependent on local hospital policy and the forms contained information that accurately assisted the consultant to do that, and only that, where they had made an independent decision to do so.

Leo considered that all of the information in the forms was accurate, balanced, complete and fully appropriate for its intended purpose and audience. Leo did not consider that dermatologists or general practitioners had been misled by the form and therefore denied a breach of Clause 7.2.

Leo submitted that high standards had been maintained at all times. As set out above, the forms were certified for a legitimate purpose; they were distributed to appropriate recipients and did not contain any misleading information. Nor were recipients requested to further distribute them in a manner that could breach local NHS restrictions or exceed their authority. Recipients were, at all times, in full control of the further distribution of this item.

Representatives were briefed as to the intended purpose, recipients and manner of use of the forms prior to their distribution; the forms were distributed in compliance with the Code. Leo submitted that the details indicated that high standards had been maintained, that there had been no breach of Clause 7.2 and, in overall conclusion, that there had been no breach of Clause 9.1.

PANEL RULING

The Panel noted that the material in question was a preprinted letter addressed 'Dear Dr' which recommended that a patient be prescribed Picato. The form had spaces for the doctor to fill in, including the patient's name, date of consultation and a tick box indicating the area requiring treatment and dosage. This was followed by details of Picato's indication and information about the phase III clinical trial data. The hospital name and department had to be provided in the top right hand corner and there was provision for the clinician's signature at the end of the letter. Prescribing information was included on the reverse.

The Panel noted that the Code did not necessarily prohibit the promotion of non-formulary medicines, but such promotion had to comply with the Code. In this regard, the Panel noted that in relation to representatives the Code stated, *inter alia*, that the arrangements in force at any particular establishment must be observed, (Clause 15.4).

The Panel noted that according to Leo, Picato was on a local CCG and trust formulary (from mid April) and that a review of a formulary submission to the local medicines management group had been deferred. The Panel noted Leo's submission that there were no published restrictions preventing the promotion of medicines prior to formulary inclusion in the five hospitals where the material was distributed. Section 4 of the local medicines management group policy: engagement with the pharmaceutical industry, in relation to sponsorship of educational meetings or the local medicines management group conference, stated that ideally the local medicines management group would prefer companies to promote mainly products included in the local formulary or those that had been approved for use within the local health economy'. The policy also set out a process for appointments with pharmaceutical company representatives and the provision of information about medicines. It did not otherwise restrict or comment on the promotion of non-formulary medicines. The local medicines management group formulary subgroup stated that the formulary was applicable to new initiations and treatments in approximately 80% of patients. In addition, the Panel noted Leo's submission that the referral footprint of dermatologists at the hospitals where the item was distributed included practices not covered by the local guidance.

The Panel noted that the complainant was concerned that the promotional material was being distributed despite Picato's non-formulary status. The Panel noted that the material in question did not comment on or raise any inferences about Picato's formulary status. The Panel did not consider that the material gave a misleading impression about Picato's formulary status and in that regard ruled no breach of Clause 7.2.

The Panel noted its comments above on the relevant requirements of the Code and local guidelines. The Panel did not consider that the company had failed to maintain high standards in this regard. No breach of Clause 9.1 was ruled.

Complaint received **13 August 2013**

Case completed **27 September 2013**

ANONYMOUS v BOEHRINGER INGELHEIM

Promotion of Spiriva Respimat

An anonymous, non-contactable general practitioner complained about what a Boehringer Ingelheim representative had said about Spiriva Respimat (tiotropium solution for inhalation) at a lunchtime meeting. The complainant alleged that in response to a query about the respimat device and its association with cardiovascular (CV) events, and without published evidence to support the claim, the representative had described the respimat device as 'perfectly safe'.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the parties' accounts differed; it was extremely difficult in such cases to know exactly what had transpired. It was unfortunate that the complainant had provided no details of the time or place of the meeting and could not be contacted. Anonymous complaints were judged on the evidence provided by the parties. A complainant had the burden of proving his/her complaint on the balance of probabilities. The representative assumed to be responsible could not recall a meeting which exactly matched the complainant's description and refuted any allegation that he/she would have described the respimat device as 'perfectly safe'.

The Panel noted that contrary to the complainant's position evidence used to support claims did not need to be published. Substantiation (including unpublished data) for any claim should be provided on request.

The Panel noted that Boehringer Ingelheim had sponsored a study to specifically investigate the CV safety of Spiriva Respimat. It had created material about the study for representatives to use only in response to questions about the CV safety of the respimat device; a leavepiece which described the study design and a briefing document which detailed Wise *et al* (2013) discussing the trial design and rationale. Neither item provided any safety results from the study in advance of their formal publication nor did they suggest that Spiriva Respimat was 'safe' or encourage representatives to describe it as such.

The Panel further noted that the complaint was dated 7 August; the study results however, had been internally embargoed until 9 September, following their official publication on 8 September. Thus when the complaint was written, and presumably when the meeting was held, the representative would not have known the study outcome.

The Panel noted that extreme dissatisfaction was usually required before an individual was moved to complain. The Panel further noted that the complainant had been very specific about what the

representative was alleged to have stated about the respimat device. However, on the basis of the information before it the Panel considered that the complainant had not demonstrated that, on the balance of probabilities, the representative had claimed that the respimat device was 'perfectly safe'. No breaches of the Code were ruled. The Panel subsequently ruled no breach of Clause 2.

An anonymous, non-contactable complainant who described him/herself as a '[named county] General Practitioner' was concerned about what a Boehringer Ingelheim Limited representative had said about Spiriva Respimat (tiotropium solution for inhalation) during a lunchtime presentation on Spiriva at his/her practice. Spiriva was also available as inhalation powder delivered via a handihaler device. Both presentations were indicated as maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD).

COMPLAINT

The complainant submitted that at the meeting he/she had raised the much publicised issues around the respimat device and its association with cardiovascular (CV) events in the context of some of the newer products on the market and the fact that other devices might offer patients a safer option. The complainant submitted that in response the representative told him/her about a new 10,000 patient study which showed that the respimat device was 'perfectly safe', however the study had not yet been published. The complainant was concerned that the representative had conveyed a message of safety with no published evidence to support it. The complainant was not clear about exactly what information could or could not be shared when there was a lack of supporting published evidence but assumed that if a company had encouraged its representatives to claim that a device previously linked with CV safety issues was now safe, it should be able to support that position with the right clinical evidence.

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 7.2, 7.4, 7.9, 15.2, 15.9, 9.1 and 2.

RESPONSE

Boehringer Ingelheim stated that it had thoroughly investigated the allegation but it noted that the complainant had provided limited details; no details of the GP practice or of the meeting date were disclosed. Boehringer Ingelheim submitted that given the complainant's anonymity, it was possible that the conversation described had not taken place in the named county. Given these challenges it was impossible to definitively identify the specific meeting.

Nonetheless, as part of Boehringer Ingelheim's internal investigation, the representative working in the county was questioned but could not recall a meeting that exactly matched that described by the complainant.

Boehringer Ingelheim explained that a retrospective pooled analyses of Spiriva Respimat studies published in 2010 found that Spiriva Respimat was associated with a non-significant numerical increase in all-cause mortality compared with placebo; a post-hoc analysis showed an excess of mortality in patients with known cardiac rhythm disorders. The Spiriva Respimat summary of product characteristics (SPC) was accordingly updated. In November 2010, a Drug Safety Update bulletin from the Medicines and Healthcare Products Regulatory Agency (MHRA) highlighted these changes and the reason for them.

Many health professionals were therefore aware of these safety concerns, and the topic was not infrequently raised with Boehringer Ingelheim representatives, including questions about any further action Boehringer Ingelheim was taking to clarify these safety concerns.

To further investigate concerns about the cardiovascular safety of Spiriva Respimat, Boehringer Ingelheim sponsored a phase IV study 'Tiotropium Safety and Performance in Respimat' (TioSPIR) which compared the efficacy and safety of Spiriva Respimat vs Spiriva Handihaler. The study had recently concluded and the abstract was posted online by the New England Journal of Medicine on 31 August 2013; the formal results would be officially announced at the European Respiratory Society (ERS) annual meeting in September 2013. The results of the TioSPIR study were internally embargoed by Boehringer Ingelheim until their official publication and had not been given to any representatives.

During questioning the representative acknowledged that a discussion initiated by a health professional regarding the cardiovascular safety of Spiriva Respimat might have prompted discussion about TioSPIR.

The representative stated that he/she would have stated that the TioSPIR study enrolled over 17,000 patients rather than the 10,000 referred to by the complainant; he/she refuted any allegation that he/she would have stated that the study showed that the respimat device was 'perfectly safe'.

The only Boehringer Ingelheim materials (copies provided) that directly related to the TioSPIR study were:

- a leavepiece which described the TioSPIR study design (ref UK/SPI – 121655). This had recently been discontinued and was withdrawn from use in August 2013.
- a briefing document for the sales teams which gave details of a recent journal publication discussing the TioSPIR trial design and rationale (ref UK/RESP – 131087).

Both of these items were intended for reactive use only, to enable representatives to respond to specific

queries about Boehringer Ingelheim's plans to obtain further clinical evidence about the safety of Spiriva Respimat, in particular whether it was associated with increased cardiovascular events.

The briefing document clarified the background and rationale for the TioSPIR study; it stated that 'In a retrospective pooled analysis of Respimat studies a numeric increase in all cause mortality was seen; the excess in mortality was observed in patients with known cardiac rhythm disorders. There was no clear rationale for this difference in mortality outcomes' and continued '... [therefore] there was a need to conduct a mortality driven endpoint trial comparing the two inhaler formations [sic].'

Both the leavepiece and the briefing document outlined the factual design of the TioSPIR study with no indication of any safety or efficacy results in advance of the formal published evidence; and there was no suggestion in either that the study showed that the Spiriva Respimat device was 'safe' nor was there any recommendation for representatives to use that term in relation to Spiriva Respimat promotion.

Boehringer Ingelheim provided the briefing material relating to the potential CV safety concerns associated with Spiriva Respimat (ref SPI/SPV 2709) which was sent to representatives in relation to the MHRA Drug Safety Update bulletin in November 2010, described above.

The briefing material did not emphasise that the Spiriva Respimat device was 'safe' nor was there any recommendation for representatives to use that term in relation to Spiriva Respimat. The emphasis was on the existing efficacy and safety profile of Spiriva in general and only passing reference was made to the TioSPIR study that would 'provide further data to enhance our understanding of the efficacy and safety of Spiriva Respimat'.

In summary, Boehringer Ingelheim could not definitively confirm the details of the complaint given the complainant's anonymity, the lack of specific information about the general practice involved and the date the alleged conversation took place. Boehringer Ingelheim submitted that it took its responsibility only to promote its medicines ethically very seriously and it refuted any allegation that it encouraged its representatives to give a message that a device, previously linked with CV safety issues, was now 'safe' based on unpublished data. Boehringer Ingelheim considered that it had provided appropriate materials and briefings for its representatives to use reactively given the potential interest in the TioSPIR data and public scrutiny of the CV risk profile of Spiriva Respimat.

Boehringer Ingelheim did not consider that there was any evidence that it had encouraged its representatives to provide misleading information about the safety of Spiriva Respimat, or encouraged the inappropriate use of the word 'safe'. In conclusion, Boehringer Ingelheim denied any breach of Clauses 7.2, 7.4, 7.9, 15.2, 15.9, 9.1 and 2. Boehringer Ingelheim refuted the complainant's allegations, and hoped that the documents provided to the PMCPA demonstrated that high standards

in relation to the promotion of Spiriva had been maintained.

In response to a request for further information Boehringer Ingelheim submitted that the TioSPIR leavepiece (ref UK/SPI – 121655) was created to form a framework for its representatives to reactively respond to queries from health professionals about what actions Boehringer Ingelheim was taking to clarify safety concerns regarding Spiriva Respimat. The representatives could therefore have only discussed information shown in the leavepiece; an overview of the study design which was freely available in the public domain at the time via clinicaltrials.gov. In addition, as stated above, Boehringer Ingelheim submitted that its representatives were subsequently provided with a briefing document about Wise *et al* (2013) which discussed the TioSPIR trial design and rationale (ref UK/RESP – 131087).

The results of the TioSPIR study were embargoed by Boehringer Ingelheim until they were officially published at the ERS annual meeting on 8 September 2013. The Boehringer Ingelheim representatives were informed of the results on 9 September.

Boehringer Ingelheim stated that when the meeting in question was held, presumably some time before 7 August when the complaint was written, no Boehringer Ingelheim representative would have been able to discuss the efficacy or safety results of the TioSPIR study as they were not available to them. The representatives would only have discussed the information available to them in the previously mentioned leavepiece and briefing document. Any additional queries about TioSPIR would have been directed to the medical information team as per their normal practice.

The leavepiece was circulated for use following the annual sales conference in January 2013 and was intended for reactive use only when health professionals queried the safety of Spiriva Respimat and asked what Boehringer Ingelheim was doing to clarify these safety concerns. The instructions for the leavepiece's use were given verbally by the scientific advisor on 31 January and to his/her recollection the briefing was as follows:

'The Spiriva sales team was informed of the medico-marketing campaign for Spiriva for 2013. They were informed that similar to previous years, Spiriva Respimat was to be promoted as another device option alongside Spiriva HandiHaler and the topic of Spiriva Respimat safety should only be discussed reactively until TioSPIR results were published in Q3 2013. The sales team were reminded that the ongoing TioSPIR trial was a ~17,000 patient trial comparing tiotropium via the HandiHaler device to tiotropium via the respimat device. In addition, the sales team were informed that that they were permitted to mention the TioSPIR trial only if they were asked by a customer what Boehringer Ingelheim were doing to address the safety concerns about Spiriva Respimat. [This

advice followed the publication of media articles expressing concern about the cardiovascular safety of Spiriva Respimat which appeared in UK medical journals in December 2012].

The sales team were informed about a TioSPIR leavepiece in development which was designed to support reactive conversations about the methodology and trial design of the TioSPIR trial. The information contained within this leavepiece was in the public domain at the time through the clinicaltrials.gov website. The sales team were reminded that the results of the TioSPIR study were anticipated to be available in Q3 2013'.

Boehringer Ingelheim noted that the Panel had noted that according to the certificate for the TioSPIR study design leavepiece its intended use was '...to allow sales teams to discuss the study with their customers to help instil confidence in the safety of the brand'. Boehringer Ingelheim clarified that the intention of the TioSPIR discussions was not to indiscriminately nor irresponsibly 'instil confidence in the safety of the brand' but to provide factual information on a reactive basis about the rationale for the TioSPIR study to further investigate the efficacy and safety of Spiriva Respimat.

Boehringer Ingelheim submitted that as previously mentioned, this information would have only been provided when health professionals queried the safety of Spiriva Respimat on a background of ongoing debate in the scientific literature and medical press, and only when health professionals asked what Boehringer Ingelheim was doing to clarify those concerns.

PANEL RULING

The Panel noted that the parties' accounts differed; it was extremely difficult in such cases to know exactly what had transpired. It was unfortunate that the complainant had not provided details of the GP practice nor the date on which the meeting at issue had taken place. The complainant was non-contactable and so the Panel could not ask him/her for more information. Anonymous complaints were judged on the evidence provided by the parties. A complainant had the burden of proving his/her complaint on the balance of probabilities. The Panel noted that the complainant had alleged that in response to a query regarding the respimat device and its association with CV events, the representative had told him/her about a new 10,000 patient study which showed that the respimat device was 'perfectly safe' despite the study not yet being published. The representative assumed to be responsible could not recall a meeting which exactly matched the complainant's description. The representative stated that, if asked he/she would have stated that the TioSPIR study enrolled over 17,000 patients rather than the 10,000 referred to by the complainant; he/she refuted any allegation that he/she would have stated that the study showed that the respimat device was 'perfectly safe'.

The Panel noted that contrary to the complainant's position, evidence used to support claims did not

need to be published. Substantiation (including unpublished data) for any claim should be provided at the request of a health professional or appropriate administrative staff.

The Panel noted Boehringer Ingelheim's submission that many health professionals were aware of the safety concerns associated with Spiriva Respimat and the topic was not infrequently raised with its representatives including questions about any further action Boehringer Ingelheim was taking to clarify those concerns.

The Panel noted that Boehringer Ingelheim had created two items related to the TioSPIR study for reactive use by its representatives in response to questions about the CV safety of the respimat device; a leavepiece which described the study design and a briefing document which detailed Wise *et al* (2013) discussing the trial design and rationale. The Panel noted that neither item provided any safety results from TioSPIR in advance of their formal publication nor did they suggest that Spiriva Respimat was 'safe' or encourage representatives to describe it as such.

The Panel further noted that the complaint was dated 7 August; the TioSPIR study results however,

had been internally embargoed until 9 September, following their official publication at the ERS annual meeting on 8 September. Thus when the complaint was written, and presumably when the meeting was held, the representative would not have known the study outcome.

The Panel noted that extreme dissatisfaction was usually required before an individual was moved to complain. The Panel further noted that the complainant had been very specific about what the representative was alleged to have stated about the respimat device. However, on the basis of the information before it the Panel considered that the complainant had not demonstrated that, on the balance of probabilities, the representative had claimed that the respimat device was 'perfectly safe'. The Panel ruled no breach of Clauses 7.2, 7.4, 7.9, 15.2 and 15.9 of the Code. The Panel subsequently ruled no breach of Clauses 9.1 and 2.

Complaint received **7 August 2013**

Case completed **2 October 2013**

ANONYMOUS v NORGINE

Promotion of Dantrolene

An anonymous, non-contactable complainant who described themselves as part of the academic anaesthetic community complained about a press release for Dantrium (dantrolene) published on Norgine Pharmaceuticals UK website. Dantrium was indicated for the treatment of malignant hyperthermia (MH).

The complainant alleged that the press release headed 'New Epidemiological Study in Malignant Hyperthermia Reinforces the Effectiveness of Dantrium (Dantrolene Sodium) in Reducing Fatal Anaesthetic Reaction' was underhand promotion. It discussed an epidemiological study of survivors which did not mention mortality data in the conclusion. The complainant further alleged that the indication for dantrolene made no reference to reduction in mortality and the press release was thus not in line with the medicine's licensed indication.

The detailed response from Norgine is given below.

The Panel noted that the press release discussed Riazi *et al.* This was an epidemiological study which examined reported data on index adverse anaesthetics and evaluated associations between complications, clinical signs and dantrolene treatment to facilitate timely clinical diagnostics and treatment of MH. The Panel noted that 57 (44.2%) of patients in the study received Dantrium after an adverse anaesthetic reaction. When the time between onset of the first clinical sign and dantrolene administration was longer, the proportion of patients experiencing a complication was also larger. Data showed that for each 10 minute delay in Dantrium administration complications increased substantially; beyond 50 minutes complications increased to 100%. There were no significant differences between the group that received and the group that did not receive Dantrium as regards duration of anaesthesia, the diagnostic test for MH susceptibility, or genetic results. The study authors discussed its limitations including data availability and that the study only looked at patients who had survived the reaction and were referred for a MH susceptibility test. Overall the authors, concurring with previous studies, concluded that early diagnosis and rapid Dantrium treatment reduced MH associated complications. The study introduction noted that studies on the incidence of adverse MH reactions demonstrated a MH morbidity rate of 35% and a MH mortality rate as high as 12%.

The Panel noted that the press release began by noting the incidence of adverse anaesthetic reactions triggered by succinylcholine alone. The press release noted that Riazi *et al* supported previous findings that early recognition and prompt administration of dantrolene was critical for patient

survival and reduction of complications. The press release stated that the 'study was worth noting because it also highlights how having Dantrolene readily available can reduce the morbidity and mortality caused by malignant hyperthermia and therefore suggests the importance of reviewing stock levels in hospitals'.

The Panel noted Norgine's submission that MH was often fatal if not effectively treated. Dantrium was the sole licensed treatment for the condition and its use was specified in multiple guidelines. It was recommended that it was a vital to stock dantrolene pre-emptively. The Panel also noted Norgine's submission that the epidemiology of MH and how dantrolene use might affect it at the population level was relatively less well studied and important new data rarely emerged. The Panel considered that in these circumstances, and given its comments on Riazi *et al* above, it was newsworthy. The Panel therefore did not consider that the press release had been released for promotional purposes only, as alleged. Nor did the Panel otherwise consider that the press release promoted Dantrium to the general public. No breach of the Code was ruled. The press release was not disguised promotion and no breach of the Code was ruled.

The Panel did not consider that the heading to the press release implied that Dantrium was licensed for reducing mortality as alleged. The heading 'New epidemiological study in malignant hyperthermia reinforces the effectiveness of Dantrium in reducing fatal anaesthetic reaction' clearly described the condition being treated, MH. The adjective 'fatal' was used to describe the trigger, an anaesthetic reaction. The Panel considered it would have been helpful to clearly state that the study was in survivors, and to state the licensed indication in the body of the press release rather than the editorial. The Panel noted the relationship between time of administration and complications. The Panel considered that whilst the statement in the press release that the study 'highlights how having Dantrolene readily available can reduce the morbidity and mortality caused by malignant hyperthermia and therefore suggests the importance of reviewing stock levels in hospitals' was not unreasonable in relation to morbidity it was not correct in relation to mortality as the retrospective study only examined data in survivors and this was not made clear. The claim was inaccurate and misleading in this regard. In the Panel's view, this misleading impression was compounded by two statements in the press release. The first paragraph of the press release which stated 'the study also further underlines that early recognition and prompt administration of dantrolene intravenous are critical for *patient survival* and reduction of complications' (emphasis added) and the quotation from a named doctor that 'These new data are very important

as they emphasize that survival from a malignant hyperthermia crisis, a rare condition, is highly dependent on early recognition and prompt action, and that the rapid use of dantrolene can ensure patient survival' (emphasis added). The Panel considered that the press release was inaccurate and therefore misleading about Riaz *et al* and mortality and breaches of the Code were ruled. The press release was not capable of substantiation in this regard; a breach of the Code was ruled. However, and on balance, the Panel did not consider that the press release implied that Dantrium was licensed to reduce mortality as alleged, nor was it inconsistent with the terms of its marketing authorisation in this regard. No breaches of the Code were ruled on this point.

The Panel considered that the company had failed to maintain high standards and a breach of the Code was ruled.

An anonymous, non-contactable complainant who described themselves as part of the academic anaesthetic community complained about a press release for Dantrium (dantrolene) published on Norgine Pharmaceuticals UK Limited's website.

COMPLAINT

The complainant noted that the dantrolene press release seen on Norgine's website on 16 August stated that a new study reinforced the effectiveness of dantrolene in reducing fatal anaesthetic reaction. On looking at the study abstract, the complainant noted that it was an epidemiological study of survivors and mortality data was not mentioned in the conclusion.

The study did not appear to have been conducted by Norgine but the complainant was unsure whether it had been involved in the study; it appeared on Norgine's website because it promoted dantrolene as part of a joint venture with another company. The complainant alleged that it was released for promotional purposes and as a private company it was not related to disclosure of corporate data.

Norgine appeared to the complainant to be a Dutch company but had UK media contact details. The complainant considered that the press release was underhand promotion that did not fulfil the requirements of an advertisement as described in the Code.

The complainant further alleged that the indication for dantrolene made no reference to reduction in mortality and the press release was thus not in line with the medicine's licensed indication.

When writing to Norgine, the Authority asked it to respond in relation to Clauses 3.2, 7.2, 7.4, 9.1, 12.1, 22.1 and 22.2.

RESPONSE

Norgine Pharmaceuticals Ltd passed the complaint to its parent company, Norgine BV, as the distributor for Dantrium.

Norgine submitted that it took the complaint and its commitment to adhere to the principles of the Code seriously. In order to provide context Norgine provided some background to the use of dantrolene IV. It was the sole licensed treatment for malignant hyperthermia (MH), originally licensed for that indication in 1980. MH was a rare but serious side effect of halothane anaesthesia which was widely recognised as being associated with high rates of mortality and morbidity. MH was often fatal if not effectively treated. Dantrolene sodium was currently the sole pharmacotherapeutic treatment for the condition, and its use was specified in multiple guidelines. Furthermore, guidelines listed dantrolene vials as one of the vital items to be pre-emptively stocked in all MH management kits at anaesthetic sites.

Norgine refuted that the press release breached the Code with respect to any of the clauses cited or otherwise.

Firstly, the press release was relevant to the use of dantrolene. This was supplied to journalists, as listed in the attachment provided and, in accordance with industry standard practice, posted on the media section of Norgine's corporate website. Being the only recognised and licensed treatment to be marketed for MH for over 30 years also meant that there was a large body of evidence to characterise the effects of dantrolene. However, the epidemiology of MH and how dantrolene use might affect it at the population level was relatively less well studied and important new data regarding the medicine rarely emerged. Moreover, since guidelines considered dantrolene to be an essential part of the clinical management of MH, it was inevitable that any large western-nation study into this condition would report on its use in that context.

Given the above, Norgine submitted that the Canadian study cited was from a significantly robust source and provided new relevant information. As such it was deemed newsworthy for appropriate dissemination. The corporate press release as a non-promotional factual communication was 'examined' rather than 'certified' according to the requirements of Clause 14.

Whilst maintaining that the press release was not promotional in nature, Norgine submitted that the reduction in mortality was consistent with the marketing authorisation for a product that treated an otherwise fatal outcome (in this case, MH) and was therefore in accordance with the terms of its marketing authorization and consistent with the particulars listed in its summary of product characteristics (SPC). Norgine therefore submitted that Clause 3.2 had been fully adhered to as the press release described Dantrium within the boundaries of its licence.

The press release did not make new claims regarding the effects of Dantrium, nor were there any statements regarding its efficacy or safety profile. Since Dantrium was indicated for the treatment of MH and was widely established as the de-facto treatment for MH crises it was used in subjects

in this epidemiological study. However, nothing additional regarding the product, over and above what was observed in the study, was communicated. The information communicated regarding delay to commencing infusion after diagnosis of a MH crisis was consistent with established knowledge about the condition and was communicated purely as an important finding of the study. Indeed, the headline clearly stated that the findings of the study 'reinforced' the already understood efficacy profile of dantrolene. In terms of overall content, Norgine submitted that the press release gave priority to the epidemiological and Dantrium related findings of the study.

Norgine submitted that there was a fair balance of information and that any claims/information were adequately substantiated in the press release, and reflected the totality of the relevant scientific evidence. Consequently Norgine submitted that the press release met the requirements of Clauses 7.2 and 7.4.

Norgine submitted that the press release was not a promotional item since it was a factual report of study findings. As such the intent was to direct it to appropriate journalists (a list of recipients was provided) and not to be communicated to the general public.

The press release was hosted on a media specific section of the company's corporate web site. In common with industry standard practice, new posts on the Norgine's corporate website were flagged on the homepage. Norgine provided screenshots of the website and details of how the document could be accessed.

Furthermore, Norgine submitted that given dantrolene's status as the sole treatment for MH, and the fact that it was invariably administered according to protocol in an emergency situation, there was almost no scope for a patient to request it or pressure a prescriber for it. Consequently, it was difficult to see why the marketing authorization holder or distributor would attempt to promote this product to the public as there would be no scope for pecuniary benefit.

The intent was solely to notify journalists with the intention of wider dissemination of the study findings in the medical press. Norgine submitted that the press release was fair and balanced in its content and reporting of the major study findings, as well as free from any product related efficacy or safety claims. Consequently, Norgine denied a breach of Clauses 9.1, 12.1, 22.1 or 22.2.

PANEL RULING

The Panel noted that Dantrium was indicated for the treatment of malignant hyperthermia which was a potentially fatal hypermetabolic reaction of skeletal muscle in response to administration of volatile anaesthetic drugs and/or depolarizing muscle relaxants.

Riazi *et al* was an epidemiological study which examined reported data on index adverse

anaesthetics and evaluated associations between complications, clinical signs and dantrolene treatment to facilitate timely clinical diagnostics and treatment of MH. The Panel noted that 57 (44.2%) of patients in the study received Dantrium after an adverse anaesthetic reaction. The medium time between onset of the first clinical sign of such a reaction and Dantrium administration was 20 minutes with a range of 12 to 70 minutes. When the time between onset of the first clinical sign and dantrolene administration was longer, the proportion of patients experiencing a complication was also larger (23.5 vs 15 minutes, $p=0.005$). Data also showed that for each 10 minute delay in Dantrium administration complications increased substantially; beyond 50 minutes complications increased to 100%. There were no significant differences between the group that received and the group that did not receive Dantrium as regards duration of anaesthesia, the diagnostic test for MH susceptibility, or genetic results. The study authors discussed its limitations including data availability and the study only looked at patients who had survived the reaction and were referred for a caffeine-halothane contracture test for MH susceptibility in North America. Overall the authors, concurring with previous studies, concluded that early diagnosis and rapid Dantrium treatment reduced MH associated complications. The study introduction noted that studies on the incidence of adverse MH reactions demonstrated a MH morbidity rate of 35% and a MH mortality rate as high as 12%.

The Panel noted that the press release was headed 'New Epidemiological Study in Malignant Hyperthermia Reinforces the Effectiveness of Dantrium (dantrolene sodium) in Reducing Fatal Anaesthetic Reaction'. The press release began by noting the incidence of adverse anaesthetic reactions triggered by succinylcholine alone. It noted that Ziari *et al* supported previous findings that early recognition and prompt administration of dantrolene was critical for patient survival and reduction of complications. Some study methodology and outcomes were outlined including the reduced incidence of complications with Dantrium and the relationship between the time of administration and complications. The press release stated that the 'study was worth noting because it also highlights how having Dantrolene readily available can reduce the morbidity and mortality caused by malignant hyperthermia and therefore suggests the importance of reviewing stock levels in hospitals'. The editorial details gave information about MH, dantrolene's licensed indication and Norgine.

The Panel noted Norgine's submission that MH was often fatal if not effectively treated. It was the sole licensed treatment for the condition and its use was specified in multiple guidelines. It was recommended that dantrolene was a vital item to be stocked pre-emptively in all MH management kits at anaesthetic sites. The Panel also noted Norgine's submission that the epidemiology of MH and how dantrolene use might affect it at the population level was relatively less well studied and important new data rarely emerged. The Panel considered that in these circumstances, and given its comments on Riazi *et al* above, the study was newsworthy. The Panel therefore did not consider that the press

release had been released for promotional purposes only, as alleged. Nor did the Panel otherwise consider that the press release promoted Dantrium to the general public. No breach of Clause 22.1 was ruled. As the press release was not promotional its nature in this regard could not be disguised, no breach of Clause 12.1 was ruled.

The Panel did not consider that the heading to the press release implied that Dantrium was licensed for reducing mortality as alleged. The heading 'New epidemiological study in malignant hyperthermia reinforces the effectiveness of Dantrium in reducing fatal anaesthetic reaction' clearly described the condition being treated, MH. The adjective 'fatal' was used to describe the trigger, an anaesthetic reaction. The Panel considered it would have been helpful to clearly state that the study was in survivors, and to state the licensed indication in the body of the press release rather than the editorial. The Panel noted the relationship demonstrated in Riazi *et al* between time of administration and complications. The Panel considered that whilst the statement in the press release that the study 'highlights how having Dantrolene readily available can reduce the morbidity and mortality caused by malignant hyperthermia and therefore suggests the importance of reviewing stock levels in hospitals' was not unreasonable in relation to morbidity it was not correct in relation to mortality as the retrospective study only examined data in survivors and this was not made clear. The claim was inaccurate and misleading in this regard. In

the Panel's view, this misleading impression was compounded by two statements in the press release. The first paragraph of the press release which stated 'the study also further underlines that early recognition and prompt administration of dantrolene intravenous are critical for *patient survival* and reduction of complications' (emphasis added) and the quotation from a named doctor that 'These new data are very important as they emphasize that survival from a malignant hyperthermia crisis, a rare condition, is highly dependent on early recognition and prompt action, and that the rapid use of dantrolene can ensure *patient survival*' (emphasis added). The Panel considered that the press release was inaccurate and therefore misleading about Riazi *et al* and mortality and ruled a breach of Clauses 7.2 and 22.2. The press release was not capable of substantiation in this regard; a breach of Clause 7.4 was ruled. However, on balance, the Panel did not consider that the press release implied that Dantrium was licensed to reduce mortality as alleged, nor was it inconsistent with the terms of its marketing authorisation in this regard. No breach of Clauses 3.2 and 7.2 were ruled on this point.

Noting its rulings above the Panel considered that the company had failed to maintain high standards and ruled a breach of Clause 9.1.

Complaint received

20 August 2013

Case completed

18 October 2013

CONSULTANT PHYSICIAN v SANOFI

Arrangements for a meeting

A consultant physician, complained about the arrangements for a meeting organised by Sanofi.

An email from Sanofi invited the recipient to attend the Lyxumia Speaker Club to discuss the key data for Lyxumia with one of the lead investigators followed by an afternoon of professional development. The email also stated that the company was able to offer to pay £1000 for attending as it viewed the meeting as preparation for any Lyxumia talks to be delivered at meetings which the local sales team would organise. Payment would be made in 2 equal amounts at the first 2 talks delivered along with honoraria.

The complainant noted that he had been offered £1,000 to attend a class on Sanofi's new medicine, Lyxumia. This was justified on the grounds that it was training to allow him to deliver talks about Lyxumia in the future. The complainant stated that he had never had any plans to talk about Lyxumia and had not requested such training. The complainant alleged that the activity was a thinly-veiled attempt to pay him to attend a meeting with the primary purpose of marketing.

The detailed response from Sanofi is set out below.

The Panel noted that according to the agenda, the meeting commenced with coffee at 9.45am. 'Workshop 1 – Lyxumia slide kit' ran from 10.00am-12.30pm, a Q&A session with the training faculty after lunch from 1.15pm-1.45pm. The development workshops ran from 1.45pm to 4.15pm with a 15 minute coffee break and included conflict management, critical appraisal of clinical papers, health economics for non economists, media training and writing successful business cases.

The Panel noted that the complainant's submission that he/she had no, nor had ever stated any, plans to talk about Lyxumia. This appeared to be contrary to Sanofi's submission that those invited had either given verbal agreement prior to being sent the email or had shown interest in being a speaker for Sanofi on another diabetes topic.

The Panel queried why Sanofi had not contracted specific speakers before inviting them to attend one of the speaker club meetings rather than broadly inviting a mixture of health professionals, some of whom might go on to carry out speaker services and some of whom might not. Nonetheless, the Panel noted that payment for attending the Lyxumia speaker club meeting would only be made to the health professional on completion of the first two speaking engagements. The payment was a fee for service. It had not been offered or promised to those attending the meeting in connection with the promotion of Lyxumia as alleged. The Panel, on this narrow ground, ruled no breach of the Code.

The Code required that the hiring of a consultant to provide a relevant service must not be an inducement to prescribe, supply, administer, recommend buy or sell a medicine. The Panel noted its comments and the ruling above of no breach in relation to the payment. Whilst the Panel had some concerns about the arrangements it did not consider that the arrangements had failed to satisfy these requirements on the narrow ground alleged. No breach was ruled.

The Panel queried whether the invitation was sufficiently clear about the arrangements. The subject title of the email read 'Lixisenatide data review meeting' and this in the Panel's view implied that it was referring to a normal promotional meeting. This impression was compounded by the first two paragraphs which described the speaker club as a discussion of the key Lyxumia data with a lead investigator. It only became clear in the third paragraph that invitees were being asked to attend as consultants and they would be paid as such. A reader glancing at the email might get the impression that a £1000 fee was payable for attending a Lyxumia promotional meeting. Indeed this was the complainant's impression. Such an impression was unacceptable. The Panel considered that Sanofi had failed to maintain high standards and a breach was ruled.

The Panel noted its rulings above and did not consider the circumstances warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure. No breach of Clause 2 was ruled.

A consultant physician, complained about the arrangements for a meeting organised by Sanofi.

An email from a Sanofi scientific advisor, diabetes, invited the recipient to attend the Lyxumia Speaker Club, which provided an opportunity to discuss the key data for Lyxumia with one of the lead investigators followed by an afternoon of professional development. The development workshops offered to attendees were conflict management, critical appraisal of clinical papers, health economics for non economists, media training, and writing successful business cases.

The email also stated that the company was able to offer to pay £1000 for attending as it viewed the meeting as preparation for any Lyxumia talks to be delivered at meetings which the local sales team would organise. Payment would be made in 2 equal amounts at the first 2 talks delivered along with honoraria.

COMPLAINT

The complainant provided a copy of an email invitation sent by Sanofi. The complainant noted

that he had been offered £1,000 to attend a class on Sanofi's new medicine, Lyxumia. This was justified on the grounds that it was training to allow him to deliver talks about Lyxumia in the future. The complainant stated that he had never had any plans to talk about Lyxumia and had not requested such training.

The complainant alleged that the activity was a thinly-veiled attempt to pay him to attend a meeting with the primary purpose of marketing.

When writing to Sanofi the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1, 18.1 and 20.1 of the Code.

RESPONSE

Sanofi explained that the Lyxumia Speaker Club was a national medical education programme designed to help and support health professionals to credibly and confidently present the clinical data and evidence for Lyxumia when engaged as speakers at Sanofi organised meetings. The particular challenge was that when Lyxumia was launched, much of the clinical data was awaiting publication. It was clear that those whom Sanofi contracted as Lyxumia speakers needed to be able to understand and articulate all of the published and unpublished data within the marketing authorization. Therefore the Speaker Club programme was devised to ensure that any speakers engaged had all the information available regarding the data and could articulate it in an appropriate way.

The identified health professionals attended a full day of training (9.45am – 4.30pm) and the agenda was identical for each meeting. The morning session related purely to Lyxumia clinical data and the afternoon session related to skills which would support the speakers in their professional capacity. The Lyxumia workshop was facilitated by a member of the training faculty, who were external experts in diabetes and experienced academic speakers. All trainers were fully conversant with the Lyxumia clinical trial data. No sales personnel attended the meetings; they were attended only by members of the medical, marketing and professional relations teams.

Sanofi provided a representatives' briefing document which outlined the process for the Speaker Club including details of how to contract the speakers and also how to identify suitable attendees. These were nominated from those areas which were most likely to have speaker meetings rather than from all areas of the UK.

There had been five meetings since March 2013 and four more were planned. Details of the venues, trainers and numbers of attendees were provided.

There was no meeting invitation for this programme as it was intended only for those who would be engaged as speakers at Sanofi meetings. It was expected that a conversation between the customer and a member of the field or medical team would take place to explore whether a given health professional would wish to speak at Sanofi meetings.

Subsequent correspondence was then sent by the head of professional relations to confirm details such as date and development course preferred, the invitation to present at two subsequent local meetings and a clear indication that payment for undertaking those engagements would be made, alongside payment for preparation time in attending the speaker training session, on completion of the speaker engagements (as per the brief).

Meeting confirmation letters were sent to health professionals who had confirmed they would like to attend before each meeting. These were personalised for the recipient by the head of professional relations and emailed to the customer.

Sanofi submitted that attendance at the Lyxumia Speaker Club was preparation for delivering subsequent talks on Lyxumia to other health professionals. Lyxumia was a new product which had recently been launched in the diabetes market of which there was little knowledge or clinical experience. The rationale for providing training was so that the clinical trial programme could be discussed and any questions the speakers might have be confidently answered by the independent external experts who made up the training faculty. Payment was offered for the time spent in the data sessions of the Speaker Club in preparation for subsequent engagements (payment was only made when the engagements had been conducted). The amount to be paid varied per health professional depending upon his/her tier of expertise using the company's UK health professional fee grid. The amount to be paid was provided to the head of professional relations once the customer was confirmed. The amount was validated against the fee grid. Therefore whilst in this case the complainant could have received £1,000, this amount could be different for other attendees. All payments offered were calculated to cover the time spent in the Lyxumia data session at the Speaker Club; it did not cover any time the speaker might have spend at any of the development sessions associated with those meetings.

Reasonable travel to attend the Speaker Club was provided as per the Sanofi UK expenses policy and was paid at the first speaker engagement the health professional undertook on the production of valid receipts.

Sanofi recognised that it was normal practice for the pharmaceutical industry to engage specialists to speak at educational events to educate other health professionals about new products. It wanted to ensure that any health professionals who spoke at Sanofi-organised and sponsored events were confident in the newly available clinical data and the evidence base for Lyxumia. It was reasonable to pay health professionals who spoke on the company's behalf for the time it took them to prepare for such meetings and Sanofi classified attendance at the morning session of this educational meeting as preparation for future speaking engagements.

No individuals were paid to merely attend the meeting. Payment was only made upon subsequent delivery of services in the form of presentation at

a Sanofi-sponsored meeting. A payment of half the allowable fee was made for each of the first two occasions the health professional spoke for the company. Any subsequent meetings (beyond the first two) would attract purely a speaking fee.

Sanofi provided a copy of its relevant standard operating procedure (SOP).

Sanofi submitted that the training faculty had all extensively been involved in Lyxumia, either as an advisory board member (UK and/or global), involved in global educational presentations or as an investigator on the ELIXA study. There was one exception to this and details were provided as were details of the possible trainers.

Some of the trainers had attended a train the trainer workshop before the first speaker workshop took place where the scientific slide deck was developed by them to ensure that it supported the clinical evidence for the product and was deemed to be credible. The initial slide kit was certified in accordance with Clause 14 for the first Speaker Club in March 2013 (GBIE.LYX.13.01.06). This set was used at the three March and April Speaker Club meetings and provided to all attendees.

Following feedback at these meetings and subsequent publication of some of the data, the slide kit was updated. A replacement slide kit (ref GBIE.LYX.13.07.08 (1)) was to be used at the September and subsequent Lyxumia speaker meetings.

The field team member in question sent emails to eight customers and had initially spoken to six out of the eight customers and gained a verbal agreement before emailing to outline the details of the Speaker Club initiative. The local Sanofi diabetes specialists had also spoken to the customers about the Speaker Club before the emails were sent. Two of the doctors had previously given consent to speak for Sanofi, not related specifically to Lyxumia, but for another diabetes topic. Details of the customers contacted were provided: six had given verbal agreement prior to sending the email.

In summary, Sanofi stated that whilst it was concerned that a health professional had gained the impression that the meeting was '... a thinly-veiled attempt to pay me to attend a meeting with the primary purpose of marketing...' it was confident that the meeting and the arrangements relating to it complied with the Code.

The meeting had significant educational content both in terms of the Lyxumia session and the afternoon sessions. The objective of the meeting was not to market the product but to ensure full understanding of the complete data set for Lyxumia, a new product, (including published and unpublished data as well as summary of product characteristics requirements) to ensure that the clinicians engaged at Sanofi-organised meetings could present data in a way that reflected the evidence base for the medicine in line with the marketing authorization. No payment was made solely to attend the meeting; payment was linked to and only paid upon provision of speaker

services. As such Sanofi did not consider that the meeting breached Clauses 2, 9.1, 18.1 or 20.1.

PANEL RULING

The Panel noted that Sanofi had not been provided with the identity of the complainant. It noted the complainant's allegation that the Lyxumia speaker club meeting was a thinly-veiled attempt to pay him to attend a meeting with the primary purpose of marketing.

The Panel examined the invitation which described the objective of the meeting as giving the health professional the opportunity to have a half day discussion on the key data for Lyxumia with one of the lead investigators and an afternoon of professional development of his/her choice. The agenda for the meeting was attached and the development workshops that could be signed up for were listed. The invitation explained that Sanofi would pay the health professional £1000 for attending as it was classed as preparation for any Lyxumia talks, organised by local sales teams, that would be delivered by the health professional. This would be paid in two equal amounts at his/her first two speaker meetings in addition to the honoraria. Travel expenses related to the Lyxumia speaker club meeting would also be paid at the first speaker meeting.

According to the agenda, the meeting commenced with coffee at 9.45am. 'Workshop 1 – Lyxumia slide kit' ran from 10.00am-12.30pm, a Q&A session with the training faculty after lunch from 1.15pm-1.45pm. The development workshops ran from 1.45pm to 4.15pm with a 15 minute coffee break. The development workshops included conflict management, critical appraisal of clinical papers, health economics for non economists, media training and writing successful business cases.

The Panel noted Sanofi's submission that attendance at the Lyxumia speaker club was preparation for speakers engaged to deliver talks on Lyxumia at Sanofi organised meetings. The Panel noted Sanofi's submission that payment was offered for time spent in the data session of the Lyxumia speaker club meeting in preparation for subsequent engagements in the form of a presentation at a Sanofi sponsored meeting and was only made in two equal amounts upon completion of each of the first two engagements.

The Panel noted the complainant's submission that he/she had no, nor had ever stated any, plans to talk about Lyxumia. This appeared to be contrary to Sanofi's submission that those invited had either given verbal agreement prior to being sent the email or if prior verbal agreement had not been given the relevant recipient had shown interest in being a speaker for Sanofi on another diabetes topic.

The Panel noted that engaging health professionals as consultants to speak at meetings was a legitimate activity. However, the arrangements had to fulfil certain criteria and otherwise comply with the Code.

The Panel noted Sanofi's submission that the objective of the meeting was not to market Lyxumia but was to ensure full understanding of the data set for Lyxumia to ensure that those clinicians that were engaged at Sanofi organised meetings could present the data in a way that reflected the evidence for the medicine in line with its marketing authorization. The Panel noted that Sanofi had run five Lyxumia Speaker Club meetings with 73 attendees and it intended to run four similar events with 3 attendees confirmed thus far. Venues included Birmingham, London, Scotland, Bristol and Leeds. The number of health professionals attending each event varied from 1 to 32. The agenda for all of the meetings were the same. The Panel queried whether the company needed in excess of 73 speakers nationally.

However, whilst at least 76 health professionals in total would have attended a Lyxumia speaker club meeting by the 5 November, not all would definitely go on to speak at a Sanofi organised meeting. With such a mixed audience Sanofi had to ensure that all of the material was appropriate for those health professionals who were not consultants; that it was all within licence and complied with the Code. The Panel queried why Sanofi had not contracted specific speakers before inviting them to attend one of the speaker club meetings rather than broadly inviting a mixture of health professionals, some of whom might go on to carry out speaker services and some of whom might not. Nonetheless, the Panel noted that payment for attending the Lyxumia speaker club meeting would only be made to the health professional on completion of the first two speaking engagements. The payment was a fee for service. It had not been offered or promised to those attending the meeting in connection with the promotion of Lyxumia as alleged. The Panel, on this narrow ground ruled no breach of Clause 18.1.

Clause 20.1 required that the hiring of a consultant to provide a relevant service must not be

an inducement to prescribe, supply, administer, recommend buy or sell a medicine. The Panel noted its comments and the ruling above of no breach of Clause 18.1 in relation to the payment. Whilst the Panel had some concerns about the arrangements it did not consider that the arrangements had failed to satisfy the requirements of Clause 20.1 on the narrow ground alleged. No breach of that clause was ruled.

The Panel queried whether the invitation was sufficiently clear about the arrangements. The subject title of the email read 'Lixisenatide data review meeting' and this in the Panel's view implied that it was referring to a normal promotional meeting. This impression was compounded by the first two paragraphs which described the speaker club as a discussion of the key Lyxumia data with a lead investigator. It only became clear in the third paragraph that invitees were being asked to attend as consultants and they would be paid as such. A reader glancing at the email might get the impression that a £1000 fee was payable for attending a Lyxumia promotional meeting. Indeed this was the complainant's impression. Such an impression was unacceptable. The Panel considered that Sanofi had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted its rulings above and did not consider the circumstances warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure. No breach of Clause 2 was ruled.

Complaint received	10 September 2013
Case completed	13 November 2013

BRISTOL-MYERS SQUIBB and ASTRAZENECA v SANOFI

Promotion of Lyxumia

Bristol-Myers Squibb and AstraZeneca jointly complained about cost comparison claims in a Lyxumia (lixisenatide) leavepiece issued by Sanofi. Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist for use in the management of type 2 diabetes.

The complainants jointly marketed Byetta (exenatide) and Bydureon (exenatide prolonged release). Exenatide was also a GLP-1 receptor agonist for use in management of type 2 diabetes. Lyxumia, Byetta and Bydureon were all add-on therapies; if required Lyxumia and Byetta could be added to insulin therapy, Bydureon could not.

Bristol-Myers Squibb and AstraZeneca stated that the leavepiece at issue compared the cost of medicines but did not provide any appropriate data on clinical efficacy and safety. This was misleading and not in the best interests of patients; the leavepiece was not sufficiently complete to enable the recipients to form their own opinion of the therapeutic value of Lyxumia. Furthermore, the claim 'Lyxumia can lower your GLP-1 prescribing costs' did not account for differences in efficacy and safety between the treatments compared. Meaningful cost savings should not be based on acquisition price alone but should take into account comparative efficacy and safety in order for both short-term and long-term cost savings to be realised. The complainants alleged that the cost savings claims were not objective and were subject to multiple caveats, which were not explained or detailed in the leavepiece. In addition, comparisons were made between medicines which were not intended for add-on to basal insulin (the focus of the leavepiece), and the comparisons could not be substantiated.

Specifically, Lyxumia vs Bydureon was not a like for like comparison, and the representation of the costs and percentage saving quoted in the leavepiece were inaccurate, unfair, misleading and could not be substantiated because:

- Bydureon was administered once weekly vs Lyxumia which was administered once a day. Bydureon was provided as four single weekly dose kits each of which contained a vial of exenatide, a syringe pre-filled with solvent, one vial connector, and two injection needles (one spare). The Lyxumia injection pen contained 14 doses but was not supplied with needles which had to be prescribed separately at an additional cost to the NHS (needle costs and dispensing charges). This was not reflected in the leavepiece.
- The recommended dose for Bydureon was 2mg exenatide once weekly with no dose titration

required. Lyxumia was started at a dose of 10mcg for the first 14 days, and then increased to 20mcg at day 15. Thus within the first 28 days of Lyxumia treatment, two different strengths need to be prescribed thus incurring two dispensing charges (the two dispensing charges would still apply if one titration pack was prescribed).

- Bydureon was not licensed for add-on to insulin but Lyxumia was. It was thus inappropriate, misleading and unfair to compare the costs of Bydureon and Lyxumia in a leavepiece which clearly promoted the use of Lyxumia as add-on to basal insulin.

The complainants further noted that guidance from the National Institute for Health and Care Excellence (NICE) stated that in order for continued treatment with GLP-1s to be justified there had to be an HbA1c reduction of 1% at 6 months. However, in the clinical trials cited in the Lyxumia summary of product characteristics (SPC), the efficacy of Lyxumia never reached a 1% reduction in HbA1c, conversely Bydureon had demonstrated >1% reduction from baseline. The leavepiece was alleged to be misleading as to the therapeutic value of Lyxumia vs the other medicines especially in the absence of any appropriate clinical efficacy data for Lyxumia.

Bristol-Myers Squibb and AstraZeneca noted that in studies in which Lyxumia was added to basal insulin, there was an increased incidence of hypoglycaemia in Lyxumia patients vs placebo. An increase in hypoglycaemia had direct cost implications in terms of increased use of blood glucose testing strips and/or hypoglycaemia rescue medicine. Conversely in a study of Byetta vs placebo when added to basal insulin, Byetta showed no increased risk of hypoglycaemia. Consequently the claim 'Lyxumia can lower your GLP-1 prescribing costs' was not objective and was indirectly misleading; choosing Lyxumia as an add-on to basal insulin would be associated with additional costs that were not reflected in the claim or the leavepiece. Bristol-Myers Squibb and AstraZeneca alleged that the claims about costs savings and reduction of prescribing costs were unfair, unbalanced, inaccurate and did not reflect the available evidence clearly. Furthermore, comparisons were made between medicines which were not intended for add-on to basal insulin (the focus of the leavepiece), and comparisons were made which could not be substantiated.

The detailed response from Sanofi is given below.

The Panel noted that comparisons based on acquisition cost alone were not prohibited by the Code. All price comparisons must be accurate, fair

and must not mislead and valid comparisons could only be made where like was compared with like. Thus price comparisons should be made on the basis of the equivalent dosage requirement for the same indications.

The front cover of the leavepiece was headed 'When it's time to add to basal insulin' and featured the strapline 'A positive addition can make all the difference'. The comparison chart at issue was headed 'LYXUMIA can lower your GLP-1 prescribing costs' and listed the 28 day acquisition cost for Lyxumia 20mcg once daily (least expensive), Byetta 10mcg twice daily, Bydureon 2mg once weekly and Victoza 1.2mg and 1.8mg once-daily. The next column listed 'savings with Lyxumia' as 15%, 26%, 26% and 51% respectively. The third and final column showed by means of a tick that Lyxumia and Byetta were 'Licensed to add-on to basal insulin' whereas Bydureon and Victoza were not. The Panel considered that it was sufficiently clear that the costs of the five medicines cited in the table were acquisition costs only and not a cost-effectiveness analysis or similar. No breach of the Code was ruled.

The Panel noted that the 28 day acquisition cost of Lyxumia did not include the additional cost of needles whereas needles were provided with and included in the cost of Bydureon. The Panel considered that the comparison with Bydureon was misleading and unfair; breaches of the Code were ruled. Similarly the claim for a 26% cost saving with Lyxumia compared with Bydureon was misleading and not capable of substantiation. Breaches of the Code were ruled.

The Panel considered that it was clear that the 28 day acquisition cost of Lyxumia given in the table was based on a dose of 20mcg once-daily; the starting dose was 10mcg daily for 14 days with the fixed maintenance dose of 20mcg once daily starting on day 15. The Panel considered that it would have been helpful if the table had stated that maintenance doses were used. Nonetheless, given that the dose was clearly stated it did not consider that the failure to include the cost of the dose titration during the first 28 days was misleading as alleged and no breach of the Code was ruled.

The Panel noted that Lyxumia and Bydureon were indicated for the treatment of adults with type 2 diabetes in combination with oral glucose-lowering medicines when adequate glycaemic control could not be achieved. However, unlike Lyxumia, Bydureon was not licensed for use in combination with basal insulin as indicated in the third column of the cost comparison table. However the Panel noted that the primary message of the leavepiece was about the use of Lyxumia as an add-on to basal insulin and it noted several references in this regard. In the Panel's view, given the context of the leavepiece, the comparison with Bydureon in the table was misleading as Bydureon was not so indicated. A breach of the Code was ruled.

The Panel noted the allegation that the leavepiece as a whole was misleading, not in the best interests

of patients and was not sufficiently complete to enable recipients to form their own opinion of the therapeutic value of Lyxumia because it compared the cost of medicines but did not include any appropriate safety or efficacy data. The Panel noted its comment above that comparisons based on acquisition cost alone were not prohibited by the Code. The Panel did not consider that the lack of clinical and safety data in that regard was misleading as alleged and thus ruled no breach of the Code.

Bristol-Myers Squibb Pharmaceuticals Limited and AstraZeneca UK Limited, jointly complained about cost comparison claims in a Lyxumia (lixisenatide) leavepiece (ref GBIE.LYX.13.04.14) issued by Sanofi. Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist for add-on use in adults with type 2 diabetes uncontrolled by oral antidiabetic medicines and/or basal insulin together with diet and exercise.

Bristol-Myers Squibb and AstraZeneca, jointly marketed Byetta (exenatide) and Bydureon (exenatide prolonged release). Exenatide was also a GLP-1 receptor agonist for add-on use in adults with type 2 diabetes who had not achieved adequate glycaemic control on maximally tolerated doses of certain oral antidiabetic medicines and had not achieved adequate glycaemic control with these agents. Bydureon, the prolonged release preparation was not indicated for add-on use with insulin.

During the course of inter-company dialogue, Sanofi withdrew a journal advertisement (ref GBIE.LYX.13.02.11) and later withdrew a Lyxumia leavepiece (ref GBIE.LYX.13.01.14) which contained claims which stated that Lyxumia provided cost-saving opportunities and 20mcg could deliver a cost saving of 15% vs Byetta 10mcg twice-daily and 26% vs Bydureon 2mg once-daily. Bristol-Myers Squibb and AstraZeneca subsequently became aware of a revised Lyxumia leavepiece (ref GBIE.LYX.13.04.14) in use; this leavepiece focussed on the use of Lyxumia as an add-on to basal insulin.

COMPLAINT

Bristol-Myers Squibb and AstraZeneca stated that the revised leavepiece, compared the cost of medicines but did not provide any appropriate data on clinical efficacy and safety. Furthermore, the claims relating to saving with Lyxumia (in the cost comparison table) and 'Lyxumia can lower your GLP-1 prescribing costs' did not account for differences in efficacy and safety between the treatments compared and was not within the spirit of Code. True cost savings which were meaningful to health professionals and payers should not be based on acquisition price alone, but must instead take into account comparative efficacy and safety data in order for both short-term and long-term cost savings to be realised. As such, the claims about cost savings were not objective and were subject to multiple caveats, which were neither explained nor detailed in the leavepiece. In addition, comparisons were made between medicines which were not intended for add-on to basal insulin (the focus of

this leaviepiece), and the comparisons could not be substantiated.

Specifically, the complainants alleged that the comparison with Bydureon was not valid, it did not compare like for like, and the representation of the costs and percentage saving quoted in the leaviepiece for Lyxumia vs Bydureon were inaccurate, unfair, misleading and could not be substantiated because:

- Bydureon was a once-weekly GLP-1 receptor agonist compared with Lyxumia which was once a day. Bydureon was provided as four single weekly dose kits each of which contained one vial of 2mg exenatide, one pre-filled syringe of 0.65ml solvent, one vial connector, and two injection needles (one spare). Lyxumia was prescribed as an injection pen containing 14 doses; needles had to be prescribed separately. As a result, for Lyxumia, the NHS had to pay the needle acquisition and dispensing costs. This was not reflected in the leaviepiece.
- The recommended dose for Bydureon was 2mg exenatide once-weekly – there was no dose titration required. Lyxumia must be started at a dose of 10mcg for the first 14 days, and then increased to 20mcg at day 15.

In addition to the acquisition costs (including needles), there were additional prescription charges to the NHS that had not been factored into the 'cost saving' calculation promoted by Sanofi. Due to the requirement for dose titration within the first 28 days when initiating treatment with Lyxumia, two different strengths need to be prescribed each of which incurred a dispensing charge (the two dispensing charges to the NHS would still apply if one titration pack was prescribed).

- Bydureon was not licensed for add-on to insulin but Lyxumia was licensed for add-on to basal insulin. Bristol-Myers Squibb and AstraZeneca alleged it was wholly inappropriate to compare the costs of Bydureon and Lyxumia in a leaviepiece clearly focussed on promoting the use of Lyxumia as add-on to basal insulin. The comparison was not on the basis of an equivalent dosage for the same indication which was misleading and unfair.

Furthermore, the complainants noted that National Institute for Health and Care Excellence (NICE) guidance stated that in order for continued treatment with GLP-1s to be justified there had to be an HbA1c reduction of 1% at 6 months. However, in the clinical trials published to date and cited in the Lyxumia summary of product characteristics (SPC), the efficacy of Lyxumia never reached a 1% reduction in HbA1c from baseline in the overall primary population studied. In contrast, Bydureon had demonstrated >1% reduction from baseline in all studies. The leaviepiece was alleged to be misleading as to the therapeutic value of Lyxumia vs the other medicines especially in the absence of any appropriate clinical efficacy data for Lyxumia.

Bristol-Myers Squibb and AstraZeneca noted that in the Lyxumia add-on to basal insulin trials (Riddle *et al* 2013a and 2013b), there was an increased incidence of symptomatic documented hypoglycaemia (blood glucose <3.3mmol/L) in patients treated with Lyxumia vs those treated with placebo. This increase in hypoglycaemia had direct cost implications in terms of increased use of blood glucose testing strips and/or hypoglycaemia rescue medicine. In contrast, in a separate clinical study of Byetta compared with placebo when added to basal insulin, there was no increased risk in hypoglycaemia seen with Byetta vs placebo. Consequently the claim 'Lyxumia can lower your GLP-1 prescribing costs' was not objective and was indirectly misleading as the choice of Lyxumia over other appropriate therapies in the add-on to basal insulin clinical setting would be associated with additional treatment-related prescribing costs which had not been reflected.

Bristol-Myers Squibb and AstraZeneca alleged that the Sanofi leaviepiece did not comply with either the spirit or the letter of the Code. Comparing costs without any consideration of clinical outcomes, the exclusion of appropriate clinical safety and efficacy data in this 'add-on to basal insulin' focussed leaviepiece and aimed as prescribers was not in the best interests of patients and meant that the leaviepiece was not sufficiently complete to allow clinicians to form their own opinion of the therapeutic value of Lyxumia. Bristol-Myers Squibb and AstraZeneca alleged that the claims about costs savings and reduced prescribing costs were unfair, unbalanced, inaccurate and did not reflect the available evidence clearly. They were therefore misleading and in breach of Clauses 7.2 and 7.3. Furthermore, comparisons were made between medicines which were not intended for add-on to basal insulin (the focus of the leaviepiece), and comparisons were made which could not be substantiated. Bristol-Myers Squibb and AstraZeneca alleged breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

Bristol-Myers Squibb and AstraZeneca knew that a similar cost comparison was ruled in breach of the Code in Case AUTH/2604/5/13, however, they considered that their concerns were wider than those at issue in that case.

RESPONSE

Sanofi explained that following the launch of Lyxumia in March 2013, it issued promotional material which included a cost comparison chart indicating the savings that could be achieved through use of Lyxumia compared with the three other GLP-1s available (exenatide, exenatide LAR and liraglutide). Although inter-company dialogue was initiated with Bristol-Myers Squibb and AstraZeneca about this table, the items were withdrawn in keeping with the undertakings given in Case AUTH/2604/5/13.

A new price comparison table was subsequently developed and included in the leaviepiece ref GBIE.LYX.13.04.14 at issue in this case. For the sake of completeness, this item was also withdrawn on 28

June 2013, in part to affect changes committed to in inter-company dialogue, and replaced by item ref GBIE.LYX.13.07.12 in August 2013.

Sanofi's response was therefore centred on item ref GBIE.LYX.13.04.14, in accordance with the complaint, but with reference to the amendments made within item ref GBIE.LYX.13.07.12, where relevant. Copies of each leavepiece were provided.

Sanofi submitted that the essence of the complaint, and of the difference in opinion between the parties, centred on the comparison made of the prescribing costs (acquisition cost) of the GLP-1 agonists. The complainants maintained that a price comparison was inappropriate as the prescriber had insufficient information on which to assess the efficacy of the products. The complaints implied that comparison of price alone, as opposed to a wider assessment of additional costs, savings and clinical outcomes of efficacy and safety, was inappropriate and that only the latter, a detailed economic evaluation, was permissible.

Sanofi submitted that the Code clearly allowed both a comparison of acquisition costs alone and a more detailed economic evaluation extending to cost effectiveness - the wider savings realised taking into account the clinical benefits and differences in resource utilisation throughout the healthcare system. Both scenarios were clearly described in the supplementary information to Clause 7.2 along with prerequisites to their use. Sanofi maintained that the price comparison table at issue clearly demonstrated the savings that could be made in acquisition cost alone with Lyxumia compared with the three other GLP-1 agonists.

Sanofi's first reference to the difference in costs between the different GLP-1 agonists was made in the leavepiece ref GBIE.LYX.13.01.14. This contained a table containing similar cost savings claims that were ruled in breach of Clauses 7.2 and 7.3 (Case AUTH/2604/5/13) and the item was therefore withdrawn in June 2013. The claims were misleading as they extended beyond acquisition cost alone.

Although never intended, Sanofi accepted the Panel's ruling and noted the Panel's opinion that it was not clear that the claims were only based on acquisition costs and not a cost-effectiveness analysis or similar.

A revised version of the table was therefore developed (leavepiece ref GBIE.LYX.13.04.14) with the express intent of leaving the reader in no doubt that the price comparison, and any savings to be made, was based on acquisition cost alone.

Sanofi submitted that the title ('Lyxumia can lower your GLP-1 prescribing costs') and table headings (including '28 day acquisition cost') made it sufficiently clear to the reader that it was a comparison of acquisition cost alone, not a wider analysis of cost savings. The title referred to GLP-1 prescribing costs, ie the direct cost to the NHS of the different medicines, and the first column referred specifically to 'acquisition cost' so as to reiterate this

point and make it clear what cost was being referred to. Costs referred to were the NHS cost within MIMS (monthly index of medical specialities), adjusted to 28 days to allow for different pack sizes. In the case of Victoza, where two different maintenance doses might be used, both were presented for the sake of completeness.

Sanofi recognised that the supplementary information to Clause 7.2 provided specific advice on making comparisons on price alone, in that comparisons could only be made 'where like is compared with like, and on the equivalent dosage for the same indication'. The four GLP-1 agonists presented in the table were all indicated for the treatment of type 2 diabetes and the costs compared were those of the maintenance dose of each for 28 days - ie the equivalent dose for the same indication. Sanofi noted that the titration doses of Byetta and Lyxumia shared the same price as the maintenance dose, so no difference existed between the two with respect to the first 2-4 weeks of treatment.

Sanofi understood from the supplementary information for a price comparison that specific conditions had to be met - that although an economic evaluation required factors including efficacy to be taken into account, a simpler price comparison required just the price per dose, where indications matched. On the basis of the shared indication for all four GLP-1 agonists, Sanofi submitted that the requirements for a price comparison to be made were met and that to claim a lower price or acquisition cost, which of itself was an important factor in the choice of medicines, was appropriate.

Sanofi recognised that in comparing price alone, there must be no allusion to wider cost savings (for example through additional prescribing of needles, internal NHS charges, nursing time in administering injections) or to benefits such as differences in efficacy or safety, as suggested. Any such allusion would amount to an 'economic evaluation', for which the Code required full consideration of the additional costs and potential savings within the wider healthcare system. Sanofi had therefore deliberately not referred to any associated costs or savings beyond acquisition of the medicine alone so as to meet the requirements of the Code regarding price comparisons. It was by intent, not by omission, that reference to additional costs was excluded - it was clear that this was a 'price comparison' and not an 'economic evaluation'. Sanofi also recognised the direct parallels between this case and Case AUTH 224/6/09 [sic], in which a price comparison table was adjudged appropriate for reasons outlined matching those above.

In summary, Sanofi recognised the difference that the Code made in presenting an 'economic evaluation' and a 'price comparison'. Sanofi submitted that it had presented a genuine price comparison, in itself recognised as a relevant factor in the choice of medicines, and had done so in compliance with the Code, and that no breach of Clause 7.2 nor 7.3 had occurred. The prices referenced in the material were an accurate

representation of the indicative cost to the NHS, adjusted to the same time period where pack sizes differed. This was the only comparison to be made, and was substantiated by the cited data on file (copy provided). The requirements of Clause 7.4 had also been met and thus no breach had occurred.

Sanofi further noted that the complainants proposed that comparison with Bydureon (exenatide LAR) was inappropriate due to the different resource utilisation associated with the use of two products (the companies cited examples of differences in needle costs and dispensing fees), and implied that it was inappropriate to present a price comparison and that only an economic evaluation was appropriate.

Sanofi agreed that were any comparison made beyond prescribing cost alone, or allusion to savings made beyond the acquisition cost, these factors would be relevant and would have to be included. However, as stated above, the comparison was clearly presented as one of price alone and savings on acquisition cost alone. The Code stipulated that both were acceptable, and Sanofi considered, as above, that as the products shared the same indication and each had a readily identifiable maintenance dose, then the conditions for presenting a price comparison were met. All four GLP-1 agonists were indicated for the treatment of type 2 diabetes (and only for the treatment of type 2 diabetes), and all, including Bydureon and Lyxumia had a clearly identifiable maintenance dose.

The choice of the usual maintenance dose (for a defined period of time) was made to represent the natural comparison that would be expected as representing equivalent dosage in the treatment of a long-term condition such as diabetes. Although in a full economic evaluation such comparison would need to take account of efficacy, the Code did not require this of a pure price comparison. Whilst it was true that for any comparison of two treatments a full economic evaluation would be likely to reveal differences in associated costs beyond the acquisition cost, to suggest that this was reason enough to prevent a comparison of cost alone was contrary to the supplementary information in the Code.

Finally, although not all GLP-1s were licensed for use with basal insulin, the fact that Lyxumia was but Bydureon was not, did not disqualify the fact that both were indicated for the treatment of type 2 diabetes. The complainants stated that reference to Bydureon in material focused on the use of Lyxumia in combination with basal insulin was unfair. Information on whether or not the product could be used with basal insulin was provided to ensure that readers were fully aware of the difference that might exist. Furthermore, no individual medicines were highlighted for specific comparison within the table - there was no invitation to draw attention to or make a comparison between any specific combinations of the listed medicines over another. Sanofi submitted that although the products might be used in different combinations (as was most often the case with this class of medicines), the shared indication meant that patients with type 2 diabetes, prior to the use of

insulin could use any of the four medicines - and that a price comparison was therefore appropriate.

In summary, the leavepiece presented a price comparison of the four GLP-1 agonists available in the UK, not an economic evaluation. All were indicated for the treatment of type-2 diabetes, and a readily identifiable maintenance dose (or doses) existed for this indication. Sanofi thus considered that the price comparison met the requirements of Clause 7.2, as outlined within the relevant supplementary information, and that as these requirements were met, the price comparison was fair and appropriate. Sanofi denied any breach of Clauses 7.2, 7.3 or 7.4.

In response to a request for further information Sanofi submitted that a wide range of needles were suitable for use with Lyxumia. A copy of the October 2012 Drug Tariff detailing the price of all needles available to be used with pre-filled injector pens was provided. Sanofi stated that it was recommended that Lyxumia be used with a 4-5mm needle which many manufacturers provided; costs ranged from £1.67 to £3.55 for 28 days. 'Auto-shield' safety needles were not routinely used for self-administration so had not been considered. Where an auto-shield needle was required, additional cost would also need to be added to Bydureon as the needle provided was not an auto-shield type. Furthermore any comparison with Byetta would need to take into account an associated doubling of needle cost given its twice daily dosing.

PANEL RULING

The Panel noted that comparisons based on acquisition cost alone were not prohibited by the Code. The supplementary information to Clause 7.2 made it clear that, as with any comparison, price comparisons must be accurate, fair and must not mislead. Valid comparisons could only be made where like was compared with like. It followed therefore that a price comparison should be made on the basis of the equivalent dosage requirement for the same indications.

The Panel noted Bristol-Myers Squibb and AstraZeneca's allegation that comparisons in the table in question were not capable of substantiation and were made between medicines that were not intended to be added on to basal insulin. Further, it was alleged that the comparison of Lyxumia with Bydureon was not a valid comparison; it did not compare like with like and the representation of the costs and percentage saving quoted in the leavepiece were inaccurate, unfair, misleading and incapable of substantiation. It was also alleged that the omission of clinical and safety data in the leavepiece as a whole rendered it incomplete as clinicians could not form their own opinion of the therapeutic value of the medicine.

The front cover of the leavepiece (GBIE.LYX.13.04.14) was headed 'When it's time to add to basal insulin' followed by a photograph of a Lyxumia pen resting on a generic device labelled 'BASAL' to make a plus sign with the strapline 'A positive addition can make

all the difference'. Page 2 was headed 'Lyxumia is a positive addition with once-daily dosing'. The comparison chart at issue appeared on the bottom half of this page and was headed 'LYXUMIA can lower your GLP-1 prescribing costs'. The table listed the 28 day acquisition cost for Lyxumia 20mcg once-daily, Byetta 10mcg twice-daily, Bydureon 2mg once-weekly, Victoza 1.2mg once-daily and Victoza 1.8mg once-daily. Lyxumia cost £54.14 and Byetta 10mcg twice-daily cost £63.69. The other medicines increased in cost. The next column listed 'Savings with Lyxumia' as 15%, 26%, 26% and 51% respectively. The third and final column showed by means of a tick that Lyxumia 20mcg once-daily and Byetta 10mcg twice-daily were 'Licensed to add-on to basal insulin' whereas Bydureon 2mg once weekly and Victoza 1.2mg once-daily and 1.8mg once-daily were not. The Panel considered that it was sufficiently clear that the costs of the five medicines cited in the table were acquisition costs only and not a cost-effectiveness analysis or similar. The Panel ruled no breach of Clauses 7.2 and 7.3 in that regard.

The Panel noted that the 28 day acquisition cost of Lyxumia cited did not include the cost of needles which had to be purchased separately whereas the Bydureon dose kit included needles. The failure to include the cost of needles rendered the comparison with Bydureon misleading and unfair. A breach of Clauses 7.2 and 7.3 was ruled. The Panel thus considered that the claim for a 26% cost saving with Lyxumia compared with Bydureon was misleading. A breach of Clauses 7.2 and 7.3 was ruled. The cost saving of 26% was not capable of substantiation and a breach of Clause 7.4 was ruled.

The Panel considered that it was clear that the 28 day acquisition cost of Lyxumia given in the table was based on a dose of 20mcg once-daily. The Panel noted the dose titration in the Lyxumia SPC, the starting dose was 10mcg daily for 14 days with the fixed maintenance dose of 20mcg once-daily starting on day 15. The Panel considered that the comparison table was clear with regard to the doses used. The Panel considered that it would have been helpful if the table had stated that maintenance doses were used. Nonetheless, given that the 20mcg dose was clearly stated it did not consider the failure to include the cost of the dose titration during the first 28 days was misleading as alleged. The Panel ruled no breach of Clauses 7.2 or 7.3.

The Panel noted that both Lyxumia and Bydureon were indicated for the treatment of adults with type 2 diabetes in combination with oral glucose-lowering medicines when adequate glycaemic control could not be achieved. However, unlike Lyxumia, Bydureon was not licensed for use in combination with basal insulin. The Panel noted that this was indicated in the third column of the cost comparison table. However the Panel noted that the primary message of the leavepiece was about the use of Lyxumia as an add-on to basal insulin. The Panel noted the references to such use on the front cover of the leavepiece as set out above. Page 2 was headed 'Lyxumia is a positive addition with once-daily dosing'. Page 3 which faced the table in question was headed 'Luxumia is a positive addition which can make all the difference' followed by a photograph of a vertical generic device labelled 'BASAL INSULIN', a photograph of a horizontal Lyxumia pen and then a photograph of the Lyxumia pen resting on the generic device labelled 'BASAL INSULIN + LYXUMIA' to make a plus sign with the strapline 'A complementary approach to significantly reduce HbA1c'. Beneath, a bullet point read 'Strong evidence supporting the use of Lyxumia as add-on to basal insulin'. In the Panel's view, given the context of the leavepiece which promoted Lyxumia as an add-on to basal insulin, the comparison with Bydureon in the table was misleading as it was not so indicated. A breach of Clauses 7.2 and 7.3 was ruled.

The Panel noted Bristol-Myers Squibb and AstraZeneca's allegation that the leavepiece as a whole was misleading, not in the best interests of patients and was not sufficiently complete to enable recipients to form their own opinion of the therapeutic value of Lyxumia because it compared the cost of medicines but did not include any appropriate safety or efficacy data. The Panel noted its comment above that comparisons based on acquisition cost alone were not prohibited by the Code. The Panel did not consider that the lack of clinical and safety data in that regard was misleading as alleged and thus ruled no breach of Clause 7.2.

Complaint received

10 September 2013

Case completed

8 November 2013

CHIEF PHARMACIST v LUNDBECK

Email promotion of Cipralex

A chief pharmacist complained about a Cipralex (escitalopram) email sent on behalf of Lundbeck.

The complainant stated that Cipralex was not on the trust formulary and Lundbeck knew that new medicines had to be introduced into the trust via the medicines committee. The complainant noted that a number of local prescribers had received the email and he/she did not find that kind of blatant advertising very helpful. The complainant had arranged for the emails to be sent to SPAM and had asked the database agency not to send any more.

The detailed response from Lundbeck is given below.

The Panel noted that the complainant appeared to be concerned that Lundbeck had used the emails to circumvent local policies which prevented representatives promoting medicines which were not on the formulary. The complainant had not alleged that the email was unsolicited.

The Panel noted that the Code did not necessarily prohibit the promotion of non-formulary medicines, but such promotion had to comply with the Code.

The Panel noted the trust's code of conduct for representatives. The policy stated that within the trust representatives might seek to inform or educate but must not promote and that they must not give educational sessions about a medicine that had not been approved by the medicines committee. The policy also set out requirements for representatives' visits, educational meetings, hospitality and meetings and samples but did not otherwise restrict or comment on any other contact a company might have with health professionals within the trust ie by direct mail or email.

With regard to the use of email, the Panel noted that the Code required a company to gain prior permission from recipients before sending them promotional emails. Where permission to use emails for promotional purposes has been given, each email should inform the recipient as to how to unsubscribe to them.

The Panel noted Lundbeck's submission that the email in question had been sent to UK health professionals registered on a database of, *inter alia*, NHS employees. When health professionals registered with the database, it was made clear that from time to time pharmaceutical promotional material might be sent. Recipients could 'opt out' of future communications which the complainant appeared to have done.

The Panel noted that the email was about the impending loss of patent on Cipralex and how that

would affect future prescribing costs; it did not refer to the local formulary status of Cipralex.

The Panel noted its comments above on the relevant requirements of the Code and the local guidelines. The Panel did not consider that the company had failed to maintain high standards in this regard. No breach of the Code was ruled.

A chief pharmacist complained about the email promotion of Cipralex (escitalopram) by Lundbeck Ltd (ref UK/ESC/1305/0409a). The email had been sent on Lundbeck's behalf by a database agency.

COMPLAINT

The complainant noted that a number of prescribers in the trust had received the promotional email at issue; the complainant noted that Cipralex was not on the trust formulary.

The complainant stated that this was the first of its kind. The complainant had contacted the database agency and asked it not to send any more emails. Other chief pharmacists in the area had also received the same email. The complainant stated that the IT department had been instructed to send the emails to SPAM.

The complainant stated that Lundbeck knew that new medicines/licences had to be introduced into the trust via the medicines committee. That kind of blatant advertising was really not helpful. The complainant provided a copy of the trust's policy for pharmaceutical product representatives.

When writing to Lundbeck, the Authority asked it to respond in relation to Clause 9.1 of the Code.

RESPONSE

Lundbeck explained that it developed the email in conjunction with a digital agency. That agency worked directly with an electronic marketing agency which owned a database of health professionals employed within the NHS and private healthcare sectors in the UK.

Lundbeck noted that the Authority recently considered the database in another complaint about Lundbeck Ltd (Case AUTH/2594/4/13) where no breach was ruled. Lundbeck submitted that the Panel's comments in that case about having to 'opt out' of emails sent using the database 'company by company' had been addressed and database users were now 'opted out' of all emails by default not just by individual company.

The database agency sent the email only to health professionals that had registered to the database

and had agreed to receive promotional emails from pharmaceutical companies. The email was sent in mid September only to psychiatrists registered with the database.

Registered database users had free access to information on the site, including information about prescription only medicines and medical devices, which could only be accessed by health professionals who prescribed these products. When registering with the database, users were informed of, and agreed to, the following statement:

'[The agency] will from time to time send information by e-mail about our associated/affiliated companies and their clients' products and services, which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information.'

Registered database users were contacted annually to confirm that their contact details were up-to-date and that they wished to continue their membership, including the receipt of promotional material from pharmaceutical companies.

In response to the specific points raised by the complainant, Lundbeck noted that the email did not relate to a new medicine or licence extension but rather to important information regarding the remaining 9 months' patent for Cipralex. Such information was often not readily available to clinicians and might be relevant when prescribing decisions were made which related to potentially long-term conditions such as major depression.

Lundbeck noted that the policy document provided by the complainant related to the activities of representatives working on the trust territory. The email in question, however, was organised by Lundbeck head office and, as such, did not come within the scope of the policy document. Lundbeck submitted that its local personnel knew about the trust policy. Consequently, there had been no local activity in the area for around a year as none of Lundbeck's current products were listed on the formulary. Lundbeck last met with the trust chief pharmacist to discuss a new product which followed the above policy recommendations.

Lundbeck submitted that high standards had been maintained and consequently there had been no breach of Clause 9.1.

PANEL RULING

The Panel noted that the complainant appeared to be concerned that Lundbeck had emailed promotional material to local health professionals in a bid to circumvent local policies which prevented representatives promoting medicines which were not on the local formulary. The complainant had not alleged that the email was unsolicited. Lundbeck

had been asked only to consider the requirements of Clause 9.1 of the Code. Lundbeck did not know the complainant's identity.

The Panel noted that the Code did not necessarily prohibit the promotion of non-formulary medicines, but such promotion had to comply with the Code. In this regard the Panel noted that, in relation to representatives, the Code stated, *inter alia*, that the arrangements in force at any particular establishment must be observed (Clause 15.4).

The Panel noted that the trust had a policy which provided a code of conduct for representatives within the trust. This stated that representatives might seek to inform or educate but must not promote. It also stated that representatives must not give educational sessions about a medicine that had not been approved by the medicines committee. The policy also set out requirements for representatives' visits, educational meetings, hospitality and meetings and samples. The policy did not otherwise restrict or comment on any other contact a company might have with health professionals within the trust ie by direct mail or email.

With regard to the use of email, the Panel noted that Clause 9.9 of the Code required a company to gain prior permission from recipients before sending them promotional material emails. Where permission to use emails for promotional purposes has been given, each email should inform the recipient as to how to unsubscribe to them.

The Panel noted Lundbeck's submission that the email in question had been sent to UK health professionals registered on a database of, *inter alia*, NHS employees. When health professionals registered with the database, they had to agree to a statement which made it clear that from time to time they might be sent pharmaceutical promotional material. If recipients no longer wished to receive emails they could 'opt out' of future communications which the complainant appeared to have done.

The Panel noted that the email was about the impending loss of patent on Cipralex and how that would affect future prescribing costs. The material did not refer to the formulary status of Cipralex within the local trust.

The Panel noted its comments above on the relevant requirements of the Code and the local guidelines. In the Panel's view the email at issue was not covered by Clause 15.4; it was sent by head office and not a representative. The Panel did not consider that the company had failed to maintain high standards in this regard. No breach of Clause 9.1 was ruled.

Complaint received	16 September 2013
Case completed	28 October 2013

VOLUNTARY ADMISSION BY NOVARTIS

Three advertisements in one journal

Novartis voluntarily admitted that the September 2013 edition of Ophthalmology Times Europe bore advertising for Lucentis (ranibizumab) on three pages.

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

Novartis noted that its global team in Switzerland, placed two separate single page advertisements in the journal at issue, on page 11 and on the inside back cover. The publisher, however, did not inform the global team that it intended to attach a false cover onto the journal and reproduce the total content of the original back cover on the false cover. There were thus now three pages in the journal which bore advertising for Lucentis, in breach of the Code. Novartis noted that the publishers had accepted full responsibility for the error.

The Panel agreed with Novartis that promotional material in the journal at issue was within the scope of the Code and it noted the sequence of events which led to three Lucentis advertisements appearing in it. The Panel noted that the publisher had accepted responsibility for the error. A breach of the Code was ruled, as acknowledged by Novartis.

Novartis Pharmaceuticals UK Ltd voluntarily admitted that the September 2013 edition of Ophthalmology Times Europe bore advertising for Lucentis (ranibizumab) on three pages.

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

VOLUNTARY ADMISSION

Novartis noted that its global team, Novartis Pharma AG Switzerland, placed two separate single page advertisements in the journal at issue, on page 11 and on the inside back cover. Global had sought and received clear guidance from the UK about the requirements of Clause 6 of the Code. The journal at issue was produced in the UK and so Novartis considered that it came within the scope of the Code.

Novartis noted that the publisher did not inform its global team that it intended to attach a false cover onto the journal and reproduce the total content of the original back cover on the false cover. There were thus now three pages in the journal which bore advertising for Lucentis, in breach of Clause 6.3. Novartis submitted that as soon as it knew of the

situation it contacted its global colleagues and a full investigation was initiated. Novartis noted that the publishers, had accepted full responsibility for the error which led to the breach of the Code. In light of this error, the global team had re-briefed teams on the UK requirements and sought reassurance from the publishers to ensure that the error could not happen again.

When writing to confirm that the matter would be taken up under the Code, the Authority asked Novartis to provide any further comments it might have in relation to Clause 6.3.

RESPONSE

Novartis had no further comments.

PANEL RULING

The Panel had first to consider whether promotional materials published in Ophthalmology Times Europe came within the scope of the Code. The publisher, editor and assistant editor were based in the UK and so in that regard the Panel agreed with Novartis' submission that the journal was within the scope of the Code.

The Panel noted that Novartis global had submitted two single page advertisements to the journal for publication in the September issue; one to appear on page 11 and the other to appear on the inside back cover. The publishers, however, printed another advertisement from another company as a false front cover which needed a corresponding extra back cover page. To create this, the publishers replicated the original back cover, effectively printing it twice. The two back covers thus contained two Lucentis advertisements. The third advertisement for the product was published as planned on page 11 of the journal. The Panel noted from an email provided by Novartis, that the publisher had accepted responsibility for the error and had acknowledged that the additional insertion of the advertisement was not paid for or requested by Novartis. Nonetheless, it was an accepted principle under the Code that pharmaceutical companies were responsible under the Code for the acts or omissions of those who worked with their authority. That three pages of the journal bore advertising for Lucentis was a clear breach of Clause 6.3 as acknowledged by Novartis; the Panel ruled accordingly. In that regard, Novartis had been let down by the publisher.

Complaint received

20 September 2013

Case completed

11 October 2013

CODE OF PRACTICE REVIEW – November 2013

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

2460/11/11	Merz/Director v Allergan	Breach of undertaking	Two breaches Clauses 2, 9.1 and 25	No Appeal Report from Panel to Appeal Board Public reprimand by Appeal Board Audit required by Appeal Board Three further re-audits required by Appeal Board	Page 3
2487/3/12 and 2489/3/12	Merz/Director v Allergan	Breaches of undertaking	Breaches Clauses 2, and 25 in each case	Appeal by respondent in both cases Report from Panel to Appeal Board Public reprimand by Appeal Board Audit required by Appeal Board Two further re-audits required by Appeal Board	Page 14
2570/12/12	GlaxoSmithKline v Napp	Flutiform leavepieces	Eight breaches Clauses 7.2 and 7.3 Six breaches Clause 7.4 Breach Clause 9.1	Appeal by complainant	Page 25
2590/3/13	Voluntary admission by Shire	Journal reprint	No breach	No appeal	Page 55
2593/4/13	Genzyme v Shire	Use of a reprint	Breaches Clauses 2, 7.2, 7.3 and 7.4	Appeal by complainant	Page 58
2600/4/13	Novo Nordisk v Sanofi	Promotion of Lyxumia	Two breaches Clause 7.2 Three breaches Clause 7.10 Breach Clause 8.1	Appeal by respondent	Page 77
2605/5/13	Anonymous v UCB	Declaration of sponsorship	No breach	No appeal	Page 87
2606/5/13	General practitioner v Takeda	Promotion of Prostag	No breach	No appeal	Page 91
2607/5/13	Pfizer v GlaxoSmithKline	Votrient leavepiece	No breach	Appeal by complainant	Page 93
2610/6/13	Warner Chilcott v Tillotts	Disguised promotion of Octasa in educational supplement	Seven breaches Clause 7.2 Three breaches Clause 7.3 Four breaches Clause 7.4 Breaches Clause 7.10 Two breaches Clause 9.1 Breaches Clauses 9.10 and 12.1	No appeal	Page 109

2611/6/13	Anonymous renal nurse v Janssen	Durogesic promotional aid	No breach	Appeal by respondent	Page 123
2612/6/13	Ex-employee v Gedeon Richter	Meeting tweets	Breaches Clauses 2, 9.1 and 22.1	No appeal	Page 126
2615/7/13	Psychiatrist v Amdipharm Mercury	Alleged unsolicited email	No breach	No appeal	Page 129
2616/7/13	Voluntary Admission by Napp	Promotional emails sent without recipient's permission	Breaches Clauses 9.1, 9.9 and 15.2	No appeal	Page 132
2619/7/13	Novo Nordisk v Sanofi	Breach of undertaking	Breaches Clauses 2, 9.1 and 25	No appeal	Page 141
2621/7/13	Anonymous v Bayer	Provision of hospitality	Breach Clause 19.1	No appeal	Page 146
2622/7/13	NHS employee v Sanofi	Conduct of representative	Breaches Clauses 2, 9.1, 9.9, 12.1 and 15.2	No appeal	Page 148
2623/7/13	Anonymous v Takeda	Promotion of Rienso	Two breaches Clause 7.2 Breach Clause 7.3 Two breaches Clause 7.4 Breaches Clauses 7.9, 7.11 and 9.1	No appeal	Page 152
2625/8/13	Anonymous v Sanofi	Conduct of representative	No breach	No appeal	Page 160
2626/8/13	Voluntary admission by Otsuka	Representative's briefing material	Breaches Clauses 14.1 and 15.4	No appeal	Page 162
2633/8/13	Medicines Management Pharmacist v Leo	Template letter to request GP initiation of Picato	No breach	No appeal	Page 165
2634/8/13	Anonymous v Boehringer Ingelheim	Promotion of Spiriva Respimat	No breach	No appeal	Page 168
2635/8/13	Anonymous v Norgine	Promotion of Dantrolene	Breaches Clauses 7.2, 7.4, 9.1 and 22.2	No appeal	Page 172
2637/9/13	Consultant Physician v Sanofi	Arrangements for a meeting	Breach Clause 9.1	No appeal	Page 176
2638/9/13 and 2639/9/13	Bristol-Myers Squibb and AstraZeneca v Sanofi	Promotion of Lyxumia	Three breaches Clauses 7.2 and 7.3 Breach Clause 7.4	No appeal	Page 180
2641/9/13	Chief Pharmacist v Lundbeck	Email promotion of Cipralext	No breach	No appeal	Page 186
2642/9/13	Voluntary Admission by Novartis	Three advertisements in one journal	Breach Clause 6.3	No appeal	Page 188

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

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

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

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines

- the provision of items for patients
- the provision of medical and educational goods and services
- grants and donations to institutions.

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

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

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

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

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

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