NUMBER 86 November 2014

CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

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.

THE 2015 CODE

Proposals for amendment of the ABPI Code and the PMCPA Constitution and Procedure were agreed at the Half Yearly Meeting of the ABPI on 20 November.

The changes to the Code come into operation on 1 January 2015 but, during the period 1 January to 30 April, no promotional material or 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.

Details of the changes together with a PowerPoint presentation and a copy of the 2014 Code are available on the PMCPA website. The interactive 2015 Code and all other supporting materials and guidance will be updated and published on the website as soon as possible.

MR PHILIP COX DSC QC

The Authority received with sadness the news that Mr Philip Cox DSC QC died on 14 November. Philip was the second independent Chairman of the Code of Practice Committee. He was appointed in 1978 and chaired that Committee until it was replaced by the Code of Practice Appeal Board in 1993. Philip retired as Chairman of the Code of Practice Appeal Board in 1999 after a total of 22 years' service.

In addition Philip chaired the ABPI IFPMA Adjudication Committee which dealt with complaints about UK companies under the IFPMA Code and the Veterinary Code of Practice Committee when it was part of the ABPI. Philip was Chairman of a World Health Organisation (WHO) Expert Group which developed the WHO Ethical Criteria for Medicinal Drug Promotion. He also had a long and successful career as a barrister.

Mr Cox was a wise, thoughtful and capable Chairman. He made a valuable contribution to the work of the Committee and the Appeal Board and was a staunch supporter of self-regulation by the pharmaceutical industry. Our thoughts are with his family at this sad time.

PUBLIC REPRIMANDS FOR GALDERMA

Galderma UK Limited has been publicly reprimanded by the Code of Practice Appeal Board for failing to provide the Authority with a full and frank disclosure of relevant information at the outset and for its fundamental lack of understanding of the Code (Cases AUTH/2684/12/13 and AUTH/2685/12/13).

In Case AUTH/2684/12/13, the Code of Practice Panel ruled breaches of the Code in relation to two unsolicited emails. In order to make its rulings, however, the Panel (and the case preparation manager) had to repeatedly ask Galderma for further information. The Panel considered that Galderma's responses demonstrated a general lack of understanding of the applicability of the Code.

The Panel reported Galderma to the Appeal Board. On consideration of that report in May 2014, the Appeal Board considered that Galderma had demonstrated significant obfuscation in its responses to the Authority and it was appalled at the company's general lack of knowledge of the requirements of the Code. The Appeal Board decided to require an audit of Galderma's procedures in relation to the Code.

The Panel also ruled breaches of the Code in Case AUTH/2685/12/13 in relation to arrangements for a meeting. The Panel considered that a number of matters demonstrated that Galderma had a very poor knowledge of the requirements of the Code and/or a reckless attitude towards its application.

The Panel reported Galderma to the Appeal Board. On consideration of that report in May 2014, the Appeal Board was appalled and extremely concerned about the materials and arrangements for the meeting. In its view there were astonishing failures at all levels. Furthermore, the Appeal Board questioned Galderma's care and attention taken in its responses to the Panel and its appeal in this case and considered that the circumstances of the meeting implied, *inter alia*, a lack of control by Galderma. The Appeal Board decided to require an audit of Galderma's procedures in relation to the Code.

Full details of Cases AUTH/2684/12/13 and AUTH/2685/12/13 can be found at pages 3 and 11 respectively of this issue of the Review.

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As Galderma subsequently declined the audit in relation to both cases and indicated that it no longer wished to accept the jurisdiction of the PMCPA, the Authority once more reported the company to the Appeal Board which decided to remove it from the list of non member companies that had agreed to comply with the Code and accept the jurisdiction of the PMCPA. The Authority advised the Medicines and Healthcare Products Regulatory Agency (MHRA) that responsibility for Galderma under the Code could no longer be accepted.

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:

Friday 26 January 2015

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 lmatthews@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

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.

ANNUAL REPORT FOR 2013

The Annual Report of the Prescription Medicines Code of Practice Authority for 2013 has been published on our website (www.pmcpa.org.uk) and copies will be sent to all who are on the mailing list for the Code of Practice Review.

There were 80 complaints in 2013 compared with 78 complaints in 2012. There were 84 complaints in 2011.

The 80 complaints in 2013 gave rise to 105 cases. The number of cases usually differs from the number of complaints, the reason being that some complaints involve more than one respondent company and some complaints do not become cases at all because they are withdrawn.

Of the 302 rulings made by the Code of Practice Panel in 2013, 264 (87%) were accepted by the parties, 28 (9%) were unsuccessfully appealed and 10 (3%) were successfully appealed. This compares with the 4% of rulings which were successfully appealed in 2012.

As is usually the case, the number of complaints made by health professionals in 2013, albeit marginally, exceeded the number made by pharmaceutical companies, there being 16 from health professionals and 15 from pharmaceutical companies.

The average time to deal with all cases in 2013 was 11.3 weeks (11.6 weeks in 2012). There was a very slight increase in the time taken for cases settled at the Panel level, 10 weeks in 2013 (9.9 weeks in 2012) and a slight decrease in the time taken for cases which were appealed, 18.1 weeks in 2013 (18.9 weeks in 2012).

Each quarter the Authority advertises brief details of cases completed in the previous three months where companies were ruled in breach of Clause 2 of the Code, were required to issue a corrective statement or were the subject of a public reprimand. These advertisements which are published on the PMCPA website and placed in the BMJ, The Pharmaceutical Journal and the Nursing Standard act as a sanction and highlight what constitutes a serious breach of the Code.

REASONS TO BE CHEERFUL

Tannyth Cox, Deputy Secretary to the Authority, gave birth in September to a boy, Zane Carter. Our congratulations go to Tannyth and her family. Tannyth will be on maternity leave until September 2015. Mrs Anne Erwin has been appointed as Interim Deputy Secretary until Tannyth returns to work.

By the end of 2014, the eight staff at the PMCPA will have collectively worked for the Authority for 100 years. Heather Simmonds, the Director, has been with the Authority since it was formed on 1 January 1993 and is thus the longest serving member of the Authority. The newest member is Tannyth Cox who joined the Authority as its Deputy Secretary in June 2013.

Heather Simmonds joined the ABPI in October 1984 and started working on the Code in 1989. Heather has now completed 30 years with the ABPI and PMCPA. Our congratulations go to Heather.

And finally, David Massam, the first Director of the PMCPA has recently celebrated his 80th birthday. David still occasionally does some work for the Authority and we wish him a very happy birthday.

CASE AUTH/2684/12/13

HEALTH PROFESSIONAL v GALDERMA

Unsolicited emails

A health professional complained about two unsolicited emails sent by Galderma (UK) on 2 April and 3 December 2013. The first email was an invitation to a symposium which was to be broadcast on 4 April as part of the Anti-aging Medicine World Congress (AMWC). The invitation referred to 'Advanced anatomy to relax, fill and care'. The second email stated that the festive season was a busy time of year for aesthetic clinics and that it was not too late to take advantage of special offers with regard to the purchase of Galderma's dermal fillers. The complainant alleged that the unsubscribe link did not work.

The complainant alleged that the reference to 'relax' in the April email clearly referred to Azzalure (botulinum toxin), used to relax muscles in the treatment of wrinkles. None of Galderma's other products had a mechanism of action which 'relaxed' anything. The complainant surmised that if mailing lists of this type were bought by Galderma, there might be recipients who were outside the licensed customer group who would be led to the company's medicines.

The detailed response from Galderma is given below.

The Panel noted that the April email was an invitation sent by a third party on behalf of the company to attend an educational symposium organised by Galderma International. The Panel noted Galderma's submission that its products, including its medicines, were mentioned throughout the session and that brand names were visible on the screen and referred to outside the auditorium.

The symposium booklet, which featured the statement 'Relax, fill and care' on the front cover, showed that one section of the symposium was entitled 'Relax and fill the upper face'. Four of the five speaker introductions referred to the use of botulinum toxin.

The Panel noted that although the symposium *per se* was not the subject of the complaint, given its content, the April email was an invitation to an event which promoted the use of Galderma's medicines. The invitation had been sent to UK health professionals and so in that regard the Panel considered that it came within the scope of the Code.

The invitation featured the statement 'Advanced anatomy to relax, fill and care' and the Panel noted Galderma's submission that 'relax' referred to the use of botulinum toxins. The Panel considered that the email, given its link to a promotional symposium and the use of the word 'relax', promoted, *inter alia*, Azzalure.

The Panel noted that Galderma was unable to provide any evidence that recipients of the email would be aware that they would be sent promotional material. The Panel was extremely concerned by Galderma's submission that neither it nor Galderma International (based in France) had taken steps to ensure that the invitation complied with the UK Code. The Panel considered that, on the balance of probabilities, Galderma had not obtained prior permission to email the invitation to those who received it and a breach was ruled. High standards had not been maintained and a further breach was ruled. These rulings were upheld on appeal.

The Panel noted that although 92% of those expected to attend the AMWC were expected to be health professionals, 8% would be others, which included, *inter alia*, distributors. The Panel queried whether distributors should have received the email given that they would not be qualified to prescribe medicines but, nonetheless, noted that there was no information before it to show that UK distributors had received the invitation. On that basis, the Panel ruled no breach of the Code.

The Panel did not consider that the use of 'relax' in association with the botulinum toxins was misleading. No breach was ruled.

The Panel noted that the December email reminded readers that special offers on the purchase of dermal fillers were available. The email referred to 'exclusive offers on the Galderma aesthetic portfolio' and so in that regard included more than just Galderma's medical devices. The end of the email stated that Galderma was the maker of, *inter alia*, Azzalure and Pliaglis (lidocaine/tetracaine). In the Panel's view the general reference to a portfolio of products and the use of the brand names of medicines meant that the email promoted medicines and so fell within the scope of the Code.

The Panel noted that prior permission was required to send emails which promoted medicines. The consent form which recipients had completed in order to receive the December email was from Q-Med, a division of Galderma, and referred to both the Q-Med range of products and products within the Galderma group. Running along the top of the form were three 'buttons' to click for more information on, *inter alia*, aesthetic medical devices; there were no buttons which related to medicines. In the Panel's view, the form did not make it abundantly clear that completion of it amounted to granting permission for promotional material about medicines to be emailed and a breach was ruled. High standards had not been maintained and a breach was ruled.

The Panel considered that, apart from the complainant's allegation, there was no information before it to show that the unsubscribe function did not work or to suggest that the email had gone to those who should not have received it. Thus no breach was ruled.

The Panel noted its rulings above with regard to both emails and considered that the matters were not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

During its consideration of this case, the Panel noted that each email should have incorporated relevant prescribing information. The Panel requested that Galderma bore this in mind for future emails. The Panel also noted its concern that neither Galderma UK nor Galderma International had taken any steps to ensure the invitation to UK health professionals to attend the Galderma symposium complied with the UK Code. In the Panel's view this showed a serious lack of understanding of the application of the Code. The Panel was also concerned that Galderma had had to be contacted a number of times before it had provided all of the relevant information. Galderma's first response was that as the complaint was about activities associated with its medical devices, it was not covered by the Code and should be closed. This was not helpful and again showed a general lack of understanding of the applicability of the Code. Self regulation relied upon full and frank disclosure at the outset.

Given Galderma's conduct in this case, the Panel reported the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for it to consider whether further sanctions were warranted.

The Appeal Board was very concerned about the number of times Galderma had had to be asked for further information; in its view there had been significant obfuscation. External confidence in self regulation relied upon companies providing a full and frank disclosure at the outset. The company's first response that the matter did not fall within the scope of the Code was incorrect and demonstrated a fundamental lack of understanding.

Overall, the Appeal Board was appalled at Galderma's general lack of knowledge of the requirements of the Code and was concerned to note that both the international and UK companies had appeared to transfer responsibility for compliance with regard to the April email to the AMWC organisers. In this regard the Appeal Board questioned how seriously Galderma UK took its own responsibilities under the Code. Galderma UK needed to be extremely diligent regarding future activities.

The Appeal Board considered that given the outcome and Galderma's conduct in relation to this case, the company should be publicly reprimanded and that its procedures in relation to the Code should be audited forthwith. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

Following notification of the Appeal Board's consideration, Galderma agreed a date for the audit but after receiving the detailed reasons it then declined to be audited or sign the requisite undertaking and assurance related to the Appeal Board rulings and it informed the Authority that it no longer accepted the jurisdiction of the PMCPA. This prompted a second report to the Appeal Board.

The Appeal Board noted that by failing to provide the requisite undertaking and assurance and declining the audit Galderma had failed to comply with the procedures set out in Paragraph 10 of the Constitution and Procedure and thus the Appeal Board decided, in accordance with Paragraph 11.4, to remove Galderma from the list of non member companies which had agreed to comply with the Code. Responsibility for Galderma under the Code could no longer be accepted. The Medicines and Healthcare Products Regulatory Agency (MHRA) and the ABPI Board of Management were subsequently advised of the Appeal Board's decision.

A health professional, complained about two emails sent by Galderma (UK) Limited on 2 April and 3 December 2013. The email of 2 April was an invitation to a live triplex symposium which was to be broadcast on 4 April as part of the Anti-aging Medicine World Congress (AMWC). The invitation referred to 'Advanced anatomy to relax, fill and care'. The email of 3 December stated that the festive season was a busy time of year for aesthetic clinics and reminded readers that it was not too late to take advantage of special offers with regard to the purchase of Galderma's dermal fillers.

In addition to dermal fillers, Galderma marketed Azzalure (botulinum toxin) and Pliaglis (lidocaine/tetracaine) both of which were medicines.

COMPLAINT

The complainant explained that he had received a number of unsolicited emails from Galderma over the course of the past year. He submitted that he had never given the company permission to email him directly. He did not believe his details should be bought by a pharmaceutical company in order to proactively contact him. The complainant considered that this type of contact was inappropriate.

The complainant alleged that the unsubscribe link did not work as he had unsubscribed and still received emails. The emails also appeared to emanate from different email addresses.

The complainant was most concerned about the reference to 'relax' in the email of 2 April and alleged that this clearly referred to Azzalure, used to relax muscles in the treatment of wrinkles. None of Galderma's other products could be described as having a mechanism of action which 'relaxed' anything. The complainant surmised that if mailing lists of this type were bought by Galderma, there might be recipients who were outside the licensed customer group who would be led to the company's medicines.

When writing to Galderma, the Authority asked it to respond in relation to Clauses 2, 3.2, 7.2, 9.1 and 9.9.

RESPONSE

Galderma stated that the email of 3 December 2013 related to the company's medical devices [Restylane and Emervel fillers] and therefore fell outside the scope of the Code. Galderma was satisfied that appropriate consent was obtained to send the email and there was a system to monitor and action requests to unsubscribe from the mailing list. After the email was sent seven recipients asked to be unsubscribed and all of them had been removed from the mailing list.

The email of 2 April 2013 was not sent by Galderma but by the organisers of the AMWC which was held in Monaco, 4-6 April 2013. Forty eight satellite symposia were held during this world congress. Galderma believed the symposium referred to on the invitation, as well as invitations for many of the other symposia held during the congress, were sent to all those registered to attend the world congress.

Galderma submitted that as the complaint related to activities associated with its medical devices which fell outside the scope of Code, it trusted that the matter could be closed. If the complainant wished to raise his concerns directly with the company it would be happy to explain what measures it had to keep its mailing list up-to-date.

In response to the case preparation manager's request for more information, Galderma stated that the email of 2 April 2013 was sent on behalf of Galderma. The company noted that this was an international meeting, the organisation and arrangement for which was carried out by its head office, Galderma International. Galderma UK was not involved in the meeting arrangements, organisation, invitations etc.

As part of the sponsorship package, sponsors were given the opportunity to send mailings to attendees. The invitation to the Galderma symposium, which was held during the world congress, was sent by the AMWC organisers to all registered attendees. Galderma had no access to the AMWC database of registered attendees and had no control over the addition or removal of recipients included in this database. The invitation was an electronic copy of an invitation distributed from the Galderma stand at the congress.

Galderma explained that the AMWC was an international meeting held in Monaco and neither Galderma International nor Galderma UK took any steps to ensure that the invitation complied with the Code as the ABPI Code was not applicable. Galderma International, however, reviewed the material to ensure that it complied with the appropriate regulations in Monaco.

Galderma submitted that unsubscribing from the AMWC mailing list would not automatically result in unsubscribing from the mailing lists of all the companies which exhibited at the AMWC. The complaint related to receipt of unsolicited emails from Galderma. As stated above, the symposium invitation (email dated 2 April) was not sent by Galderma UK, the other email of 3 December related to information about medical devices and therefore fell outside the scope of the Code. Nevertheless, Galderma was satisfied that it had obtained appropriate consent to send the email of 3 December and it had a system in place to monitor and action requests to unsubscribe from its mailing list. As stated above following the email sent on 3 December, seven requests to unsubscribe were received and had all been actioned.

In response to another request from the case preparation manager for further information, Galderma stated the email of 2 April was sent on behalf of Galderma International. As stated above, the email was an electronic copy of a paper invitation distributed from the Galderma stand at the congress. The electronic copy was provided to the AMWC organisers by Galderma International and had been approved by Galderma International. Information from the AMWC organisers described the profile of attending delegates as dermatologists (30%), plastic and cosmetic surgeons (20%), anti-aging doctors and other specialities (gynaecologists, endocrinologists etc) (30%), aesthetic and general practitioners (12%), and others such as medical allied health, nurses, clinic managers, distributers etc (8%). Galderma International was therefore satisfied that delegates to the AMWC were of an appropriate professional status to receive such mailings.

Galderma International's sponsorship package included three emailings. Thirty four Galderma UK sponsored health professionals attended the congress. Galderma UK did not know how many UK delegates attended the congress but information from the AMWC organisers showed that 7,369 delegates attended the 2012 AMWC. Attendance was expected to exceed 8,000 in 2013, 45% of which were expected from western Europe. The symposium was organised by Galderma International, however, Galderma UK sponsored thirty four delegates to attend the congress, although it did not know how many, if any of these, attended the symposium. Attendance at the Galderma International symposium was not a condition of sponsorship to attend the congress. Five Galderma UK staff attended the AMWC congress and were present on the Galderma exhibition stand at various times during the congress.

Galderma International confirmed to Galderma that it was satisfied that appropriate consent was obtained by the AMWC organisers (as part of the registration process) to send such emails and the emails were sent to appropriate recipients. Galderma denied any breach of the Code.

In response to a request from the Panel for more information and its observation that a statement at the end of the email of 3 December referred to Galderma, the makers of, *inter alia*, Azzalure and Pliaglis, Galderma maintained that the email related to its medical devices. 'Galderma, the makers of, *inter alia*, Azzalure and Pliaglis', was a statement of fact that appeared outside the main body of the text. The sentence listed all of Galderma's

aesthetic product range irrespective of legal status. Galderma failed to see how this could be considered promotional or in breach of the Code. That said, the company had a robust system in place to collect consent and to manage requests to unsubscribe. Galderma provided a screen shot from its website for those who wanted to sign up to receive product news and information on promotional offers by post, email and text.

With regard to the email of 2 April, Galderma reiterated that it was sent by the AMWC organisers; it was not sent by Galderma or using the Galderma database. Therefore, a request to unsubscribe from this email would not automatically unsubscribe the recipient from all other company mailing lists. Whilst Galderma had complete confidence in its system, following the complaint it checked that the unsubscribe function operated effectively. The test indicated no problems and that, together with the fact that no recipients had reported any problems with the unsubscribe function, further supported its confidence in the system.

Galderma stated that it did not have access to the registration paperwork used by the AMWC organisers. However, it had been advised that registration included access to sessions, workshops, exhibition, certificates of attendance, congress bag and all congress documents/material. Galderma noted the following legal information from the AMWC organisers:

> 'PERSONAL DATA
> The website [web address given] is declared to the National Commission of Information and Liberties, under the number 1375031. Your data subscribed on our website are aimed to be used by our Administrative Secretariat only. This data will of course not be given up or sold to any external company or person. In compliance with the French internal legislation, you could modify, suppress or change any of your data (art.34 of the law – informatique et Libertes – dated 06.01.1978). To exercise this right, contact: [email address given].'

Galderma submitted that the AMWC organisers arranged many congresses throughout the world. Exhibiting at the congress and utilising the congress resources was a service that pharmaceutical companies paid for. There was no reason to believe that the organisers had not fulfilled their professional duty to keep mailing lists up-to-date by acting upon requests to unsubscribe.

Galderma stated that the objective of its symposium was to provide training on the anatomical structures involved in various facial aesthetic procedures with particular reference to its products. Galderma provided details of the two hour session. Live procedures were carried out in the auditorium which was televised on a large screen. On a parallel screen, a surgeon showed the anatomical features (fat tissue, skin layers, nerves, blood vessels etc) involved in the procedure using a cadaver broadcast live from France. The symposium was organised by Galderma International and Galderma products (medical devices and medicines) were mentioned throughout the session. The brand names of Galderma products were also visible on the screen as well as outside the auditorium. Galderma UK did not have a copy of the symposium. Galderma noted that the content of the symposium was not the subject of the complaint and so it queried why the Panel had requested a recorded copy.

Galderma referred to the symposium objective as stated above and the reference to Galderma products and stated that within that context 'relax' in the statement 'Advanced anatomy to relax, fill and care' referred to the effects of botulinum toxins, 'fill' referred to the effects of dermal filler as did 'care'.

Galderma noted that the complaint related to the failure to action a request to unsubscribe, receipt of the unsolicited emails and use of the word 'relax', all of which it considered had been addressed. The company repeated that, in its view, the activities at issue did not fall within the scope of the Code and even if they did there was no breach.

In response to a further request from the Panel for more information, Galderma submitted that Galderma International was based in France.

With regard to Q-Med, Galderma explained that it acquired the company and its full range of aesthetic medical devices in 2011. The Q-Med product range which consisted of Restylane and Macrolane (medical devices) and Restylane SkinCare (cosmetic) was integrated into the Galderma aesthetic portfolio which consisted of Emervel (medical device) and Azzalure and Pliaglis (prescription only medicines). The reference to the Galderma group of products, on the health professionals' consent to receive emails form, referred to all of these products and any future additions to the aesthetic portfolio.

PANEL RULING

With regard to Galderma's concern that it had been asked for information which went beyond the scope of the complaint, the Panel noted that the details requested had not been sought in order to widen the scope of the complaint but to ensure that the Panel fully understood the context in which the two emails had been sent.

The Panel noted that the email of 2 April 2013 was an invitation to attend an educational symposium organised by Galderma International. The email had been sent by a third party on behalf of the company. The Panel noted Galderma's submission that during the symposium, Galderma products, including its medicines, were mentioned throughout the session and that brand names were visible on the screen and referred to outside the auditorium.

The symposium booklet, which featured the statement 'Relax, fill and care' on the front cover, showed that one section of the symposium was entitled 'Relax and fill the upper face'. In four of the five speaker introductions, the use of botulinum toxin was referred to.

The Panel noted that although the symposium *per se* was not the subject of the complaint, given its

content the email of 2 April 2013 was an invitation to an event which promoted the use of Galderma's medicines. The invitation had been sent to UK health professionals and so in that regard the Panel considered that it came within the scope of the Code.

The Panel noted Galderma's submission that the UK company was not involved with the meeting arrangements, organisation, invitations etc. Nonetheless, it was a well-established principle under the Code that UK companies were responsible for the acts or omissions of overseas parent companies or affiliates that came within the scope of the Code.

The invitation featured the statement 'Advanced anatomy to relax, fill and care' and the Panel noted Galderma's submission that 'relax' referred to the use of botulinum toxins. Galderma marketed Azzalure, a botulinum toxin. The Panel considered that the email, given its link to a promotional symposium and the use of the word 'relax', promoted, *inter alia*, Azzalure.

The Panel noted that the Code prohibited the use of emails to promote medicines, except with the prior permission of the recipient. Previous cases had established that text or dialogue requesting permission to send promotional material had to make it abundantly clear that the intention was to send promotional material from pharmaceutical companies about medicines.

The Panel noted, as stated above, Galderma's responsibility for the UK use of the email. The company was unable to provide any evidence that recipients of the email would be aware that they would be sent promotional material. The Panel was extremely concerned by Galderma's submission that neither it nor Galderma International (based in France) had taken steps to ensure that the invitation complied with the UK Code. The Panel considered that, on the balance of probabilities, Galderma had not obtained prior permission to email the invitation to those who received it. A breach of Clause 9.9 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. These rulings were appealed.

The Panel noted the demographics of those expected to attend the AMWC and that although 92% were expected to be health professionals, 8% would be others, which although they included nurses, also included medical allied health, clinical managers, distributors etc. Galderma International was satisfied that the all delegates were of an appropriate professional status to receive the emailed invitation. The Panel queried whether, in particular, distributors should have received the email given that they would not be qualified to prescribe medicines but, nonetheless, noted that there was no information before it to show that UK distributors had received the invitation. On that basis, the Panel ruled no breach of Clause 3.2.

The Panel noted that 'relax' had been used in association with the botulinum toxins and in that regard did not consider that its use was misleading. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above with regard to the email of 2 April and considered that the matter was not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Turning to the email of 3 December, the Panel noted that it was sent to remind readers that special offers on the purchase of dermal fillers were available. The email referred to 'exclusive offers on the Galderma aesthetic portfolio' and so in that regard included more than just Galderma's medical devices. A statement at the end of the email stated that Galderma was the maker of, *inter alia*, Azzalure and Pliaglis. In the Panel's view the general reference to a portfolio of products and the use of the brand names of medicines meant that the email was not limited to medical devices; it promoted medicines and so fell within the scope of the Code.

The Panel noted its comments above regarding the prior permission required to send emails which promoted medicines. The consent form which recipients had completed in order to receive the email at issue was from Q-Med, a division of Galderma. The form referred to both the Q-Med range of products and products within the Galderma group. Running along the top of the form were three 'buttons' to click for more information on, *inter alia*, Restylane, Emervel and Macrolane; there were no buttons which related to medicines. In the Panel's view, the form did not make it abundantly clear that completion of it amounted to granting permission for promotional material about medicines to be emailed. A breach of Clause 9.9 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted the complainant's allegations that the unsubscribe link did not work. Galderma had stated, however, that after the email had been sent, seven recipients asked to be unsubscribed from the mailing list and this had been actioned. The Panel considered that, apart from the complainant's allegation, there was no information before it to show that, on the balance of probabilities, the unsubscribe function did not work. No breach of Clause 9.9 was ruled.

The complainant had made a general allegation, based on Galderma's purchase of mailing lists, (which the Panel assumed applied to both emails at issue) that some recipients of the email of 3 December might have been outwith the licensed customer group, but had produced no evidence to show that this was so. A complainant had the burden of proving his/her complaint on the balance of probabilities. The Panel considered that no evidence had been provided to suggest that the December email had gone to those who should not have received it. No breach of Clause 3.2 was ruled.

The Panel noted its rulings above with regard to the email of 3 December and considered that the matter

was not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

During its consideration of this case, the Panel noted that given its view that both emails were promotional, each should have incorporated relevant prescribing information. The Panel requested that Galderma bore this in mind for future emails. The Panel also noted its concern that neither Galderma UK nor Galderma International had taken any steps to ensure the invitation to UK health professionals to attend the Galderma symposium complied with the UK Code. In the Panel's view this showed a serious lack of understanding of the application of the Code. The Panel was also concerned that the case preparation manager and the Panel had had to contact Galderma a number of times before the company had provided all of the relevant information. Galderma's first response was that as the complaint was about activities associated with its medical devices, it was not covered by the Code and should be closed. This was not helpful and again showed a general lack of understanding of the applicability of the Code. Self regulation relied upon full and frank disclosure at the outset.

The Panel considered Galderma's conduct in this case warranted consideration by the Code of Practice Appeal Board and decided to report the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for it to consider whether further sanctions were warranted.

APPEAL BY GALDERMA

Galderma appealed the Panel's ruling of breaches of Clauses 9.1 and 9.9 in relation to the email invitation of 2 April 2013.

Galderma submitted that the Panel had operated under a misapprehension with regard to the email from the AMWC organisers. Whilst Galderma had previously acknowledged that Galderma International approved the email, that document was not itself at issue.

Galderma submitted that what was at issue was who controlled the mailing. The AMWC was a large and long-running (13 years) international event with a high ethical and scientific reputation with delegates from some 40 nations. As was normally the case with such conferences, the organisers would have invited every delegate to every session. Galderma was not allowed to know, under data privacy law, the identity of the recipients; it thus had no control over the mailing or the selection of recipients.

Galderma submitted that the Panel's potential misunderstanding was evidenced in its ruling and its statement that 'Galderma had not obtained prior permission to email the invitation to those who received it'. As stated above, Galderma was not allowed to access the mailing list in any way.

Galderma submitted that it was unrealistic to suggest that it should have second-guessed the AMWC organisers about their data protection consent forms. Galderma referred to the AMWC notice quoted above and like every other company involved, Galderma considered that it had conducted due diligence and was entitled to rely on the adequacy of the consent procedures of the AMWC organisers. The content and procedures of AMWC communications were approved under applicable French law and codes (which reflected the EFPIA Code).

Galderma noted that under Clause 23.6 of the Code, 'Companies are responsible for information about their products which is issued by their public relations agencies' and queried whether the Panel had drawn an analogy to this sort of situation. If so, this was not an analagous situation as the AMWC, unlike a public relations agency, did not do Galderma's bidding, and as noted above, it had operated in this regard, totally at arm's length from Galderma and other participating companies.

Galderma submitted that it was important to analyse what a ruling of a breach of Clause 9.9 meant and whether undertakings to this effect could be observed in practice. Galderma understood and agreed that it was a well established principle under the Code that a UK company was responsible for the acts and omissions of overseas parent companies of affiliates. However, as noted above, this could only be the case where the company had control or transparency of the situation.

Galderma submitted that for example, if UK physicians decided to attend an international conference held outside the UK, with no direct involvement of the UK company, (the company being represented by either the non UK head office or a local affiliate by way of a stand and/or symposium), it would seem absurd for the UK company to be responsible for activities related to those attendees. If this were so then documentation and proceedings for all meetings held anywhere in the world, where UK physicians could potentially attend, would need to be certified in the UK to ensure that all activities complied with the UK Code, just in case a UK physician decided to attend the meeting.

In summary Galderma submitted that what the Panel appeared to be asking of it in the AMWC situation was unachievable in practical terms. Galderma could not therefore be considered to be in breach of Clause 9.9 nor, accordingly, in breach of Clause 9.1.

COMMENTS FROM THE COMPLAINANT

The complainant had no comment on Galderma's appeal.

APPEAL BOARD RULING

The Appeal Board noted that Galderma International had sponsored the AMWC and that, as part of the sponsorship package, the organisers would send three emails on behalf of the company to congress attendees. The email at issue, dated 2 April 2013, was one of those emails and was an invitation to a Galderma promotional symposium. The email had been paid for and approved by Galderma International and so in that regard the Appeal Board

considered that the company was inextricably linked to it and thus responsible for controlling it and ensuring that it met the requirements of the codes in every country to which it was sent. The company could not transfer responsibility for compliance to the conference organisers. In sending the email, the AMWC organisers had not operated at arm's length from Galderma as submitted.

The Appeal Board noted that as the meeting at issue was a major international congress held in Europe, attendance of UK health professionals (even in addition to the thirty four sponsored to attend by Galderma UK) was to be expected. In that regard Galderma International should have consulted its UK colleagues to ensure that when the congress organisers sent the email to invite UK health professionals to a Galderma symposium, it met the requirements of the UK Code. The Appeal Board was extremely concerned to note that neither Galderma International nor Galderma UK had taken any steps to ensure that the email at issue, when sent to UK health professionals, complied with the UK Code. The Appeal Board considered that although Galderma International should have consulted its UK company with regard to compliance with the UK Code, Galderma UK for its part had sponsored UK health professionals to attend the congress and so it should have been more proactive and worked with its international colleagues to ensure that where applicable, materials and activities complied with the UK Code.

The Appeal Board noted that it was a well established principle under the Code that UK companies were responsible for the acts or omissions of overseas parent companies or affiliates that came within the scope of the Code. The email at issue, sent to UK health professionals, came within the scope of the Code. Galderma had provided no additional evidence in its appeal to show that those who had received the email had given prior permission for the email to be sent. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.9. High standards had not been maintained and the Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal was unsuccessful.

COMMENTS FROM GALDERMA ON THE REPORT

At the consideration of the report, the Galderma representative submitted that the company had made a number of mistakes and it apologised. The Galderma representative stated that this was the first complaint about Galderma for ten years. Thus the company had not been through the process for a long time. Lessons had been learnt and changes had and would be made to address the issues raised.

[Post meeting note: The last complaint about Galderma was in 2007 (Case AUTH/2019/7/07). The last report about Galderma was considered by the Appeal Board in 2003 (Case AUTH/1281/2/02)]

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board was very concerned about the number of times the case preparation manager and the Panel had had to ask Galderma for further information. In the Appeal Board's view there had been significant obfuscation. External confidence in self regulation relied upon companies providing a full and frank disclosure at the outset. The company's original response that the matter related only to medical devices and did not fall within the scope of the Code was incorrect and demonstrated a fundamental lack of understanding.

The Appeal Board was extremely concerned to note from questioning the Galderma representative that the company did not have a key standard operating procedure (SOP) relating to a matter in question. The Appeal Board considered that, as a matter of urgency, the company must put in place procedures so that it was confident that, where applicable, future arrangements complied with the UK Code.

Overall, the Appeal Board was appalled at Galderma's general lack of knowledge of the requirements of the Code and was concerned to note that both the international and UK companies had appeared to transfer responsibility for compliance with regard to the email of 2 April, 2013, to the AMWC organisers. In this regard the Appeal Board questioned how seriously Galderma UK took its own responsibilities under the Code. Galderma UK needed to be extremely diligent regarding future activities.

The Appeal Board considered that the outcome and Galderma's conduct in relation to this case warranted the imposition of further sanctions. The Appeal Board decided that the company should be publicly reprimanded and that its procedures in relation to the Code should be audited as soon as was practically possible. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

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Following notification of the Appeal Board's consideration, Galderma agreed a date for the audit.

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COMMENTS FROM GALDERMA

Following receipt of the details of the Appeal Board's consideration, Galderma reiterated that it was one of 34 sponsors of the AMWC. The process of obtaining consent adopted by the AMWC organisers would have been the same in relation to all mailings to all the AMWC delegates and accordingly any sponsor whose products included medicinal products would be as guilty as Galderma of the breaches of the Code ruled by the Panel and the Appeal Board. Moreover Galderma understood that all the attending delegates had indicated to the AMWC that they were prepared to receive information and emails from the AMWC about the congress events.

Moreover Galderma disagreed that using the symposium title in an invitation to a sponsored symposium itself promoted a specific prescription medicine. All sponsored symposia required a title. This title was used in the official agenda programme

books. Delegates used this title to determine their attendance or not. Congress organisers relied on companies to sponsor symposia at their congresses to help fund the scientific content of the congress.

Galderma considered that the intent of a public reprimand for this alleged infringement was excessive.

Galderma extremely strongly considered that the Panel and the Appeal Board had not given it a fair hearing on this matter and thus it gave notice that it would no longer submit to the jurisdiction of the PMCPA and would not undergo the audit.

Galderma fully anticipated that once the PMCPA had advised the MHRA of the company's decision to withdraw from the PMCPA's jurisdiction, the MHRA might wish to conduct an audit of a similar nature and/or take other measures and it was quite prepared to undergo this.

Under the MHRA Galderma submitted that it could continue to observe the provisions of the Code so far as they reflected advertising regulations and the MHRA Blue Guide.

With regard to the fairness of Galderma's hearing, the company did not see any benefit in reiterating its previous arguments in the light of its decision to resign from the jurisdiction of the PMCPA.

In the light of its resignation from the PMCPA's jurisdiction, Galderma knew of, and was comfortable with the Appeal Board's right under the provisions of Paragraph 11.4 of the Constitution and Procedure to remove the company from the list of non member companies which had agreed to comply with the Code and advise the MHRA that responsibility for Galderma under the Code could no longer be accepted. Galderma further noted that such action was required in accordance with the 3 November 2005 Memorandum of Understanding between the ABPI, PMCPA and MHRA. Galderma acknowledged the PMCPA's obligation to notify the ABPI Board of Management that such action had been taken.

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In accordance with Paragraph 11.1 of the Constitution and Procedure the Authority reported Galderma to the Code of Practice Appeal Board for it to decide whether to remove the company from the list of non member companies which had agreed to comply with the Code and advise the Medicines and Healthcare Products Regulatory Agency (MHRA) that responsibility for Galderma under the Code could no longer be accepted (Paragraph 11.4 of the Constitution and Procedure).

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APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE AUTHORITY

The Appeal Board noted that Galderma had asked to be removed from the list of non member companies that had agreed to comply with the Code.

The Appeal Board noted that the Director had asked Galderma for further details as to why it considered that the 'Panel and Appeal Board have failed to give Galderma a fair hearing on this matter…'. The Appeal Board considered this was a very serious allegation, particularly as the PMCPA had followed its Constitution and Procedure in dealing with this case. Galderma had not provided further detail.

The Appeal Board noted that by failing to provide the requisite undertaking and assurance and declining the audit Galderma had failed to comply with the procedures set out in Paragraph 10 of the Constitution and Procedure and thus the Appeal Board decided, in accordance with Paragraph 11.4, to remove Galderma from the list of non member companies which had agreed to comply with the Code. Responsibility for Galderma under the Code could no longer be accepted. The MHRA and ABPI Board of Management were subsequently advised of the Appeal Board's decision.

Complaint received	**11 December 2013**
Undertaking received for matters not appealed	**15 April 2014**
Appeal considered	**15 May 2014**
Report to Appeal Board	**15 May 2014, 24 July 2014**
MHRA informed	**4 August 2014**
ABPI Board informed	**4 August 2014**

CASE AUTH/2685/12/13

ANONYMOUS, NON CONTACTABLE NURSE v GALDERMA

Meeting arrangements

An anonymous, non-contactable complainant who described him/herself as a registered nurse complained about arrangements for an educational meeting about aesthetics organised by Galderma (UK) in association with a nurse support group. The complainant provided the agenda which listed four presentations, two of which were particularly relevant to medicines marketed by Galderma; one was about botulinum toxins (Galderma marketed Azzalure) and the second was about the company's product Pliaglis (tetracaine/lidocaine), a topical anaesthetic for use in dermatological procedures. The covering letter sent with the agenda stated that there was no meeting charge for members of the nurse support group but 'due to the high calibre of the speakers provided by Galderma you are required to have purchased a minimum of Two Emervel Classics from [named pharmacy] between now and the 16th November 2013'.

The complainant was disgusted that he/she was forced to buy at least two boxes of Galderma's dermal fillers to be able to attend. The complainant submitted that firstly it was just wrong and, secondly, he/she did not like or use the particular filler, and thirdly was not even trained on it.

The complainant submitted that these actions did not do the industry any favours and just lowered standards, which was exactly the opposite of what he/she hoped to achieve.

The detailed response from Galderma is given below.

The Panel disagreed with Galderma's submission that as the complaint specifically concerned the 'purchase of a medical device' in relation to attendance at an event which focused on medical devices it did not fall within the scope of the Code. The Panel noted that the Code applied, *inter alia*, to the promotion of medicines to health professionals. The Panel noted that the agenda included a presentation on botulinum toxins in aesthetics which compared the available products including Azzalure and a presentation on Pliaglis by a Galderma employee. A Pliaglis leavepiece was also available. In addition, the Panel noted that the agenda stated that the meeting provided 'an opportunity to present evidence in your prescribing portfolio relating to Toxin'. The Panel considered that the meeting clearly promoted Galderma's prescription only medicines and in this regard noted that the complainant had attended because he/she was particularly interested in the presentation on botulinum toxins.

The Panel noted that Galderma had, *inter alia*, contacted and verbally finalised arrangements and paid the speakers, two of whom were suggested by the nurse support group including a consultant oculoplastic surgeon and a senior aesthetic product developer with Galderma. Galderma provided an additional internal speaker, sourced and funded the venue, drafted and provided the flyer and agenda to the nurse support group for distribution and provided general support. The covering email to the agenda, drafted by the nurse support group described the event as a 'Galderma educational day'. Seven Galderma staff attended including five sales staff. The Panel considered that given Galderma's role and the content of the meeting, the matter of complaint came within the scope of the Code.

Whilst noting that elements of the meeting referred to medical devices, the Panel considered that the content in relation to prescription only medicines and the overall meeting arrangements had to comply with the Code. This would include the requirement for delegates to purchase a product before attending. If the meeting content was only about medical devices then it was likely that the Code would not apply.

The Panel noted that the email sent with the agenda stated that there was no charge for the meeting but certain purchases were required. The covering letter further stated that '[named pharmacy] have kindly confirmed a special offer price for us all of £74.34 per box. You will also receive a free Restylane Skin Booster and complimentaries on the day. For a cost of £150 we get a fabulous deal, equivalent to £240 worth of products plus the meeting'. Delegates had to bring their invoices to the conference as proof of purchase to gain entry. Attendees who were not members of the nurse support group were charged £40 to attend and were also required to purchase 2 packs from the named pharmacy. The Panel noted Galderma's submission that it was not uncommon within the aesthetics industry for there to be a requirement to purchase a product before attending educational or training sessions. The Panel noted its finding above that the overall arrangements had to comply with the Code. It could also be argued that attendees were paid £90 to listen to talks promoting medicines. The Panel considered that the discount offered on the obligatory purchase of Emervel together with the items received on the day meant that attendees were given a pecuniary advantage of a minimum of £90 in connection with the promotion of Azzalure and Pliaglis and a breach of the Code was ruled.

The Panel considered that patient safety was extremely important and was concerned about patient safety given that a health professional was required to purchase a product that he/she knew nothing about and upon which he/she was not trained. No training was provided at the meeting. In addition paying health professionals to attend

promotional meetings was unacceptable. The Panel considered that overall high standards had not been maintained and a breach was ruled. In addition the Panel considered that the circumstances were such that Galderma had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

Given Galderma's conduct in this case, the Panel reported the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for it to consider whether further sanctions were warranted.

Upon appeal the Appeal Board noted that in Galderma's view as long as a health professional knew the general technique for injecting dermal fillers, not being trained to administer a specific filler did not have adverse implications for patient safety and thus the Panel's ruling was based on a misunderstanding. The Appeal Board noted, however, that the ruling of a breach of Clause 2 referred to all the circumstances of the case, it was not limited to matters of patient safety.

The Appeal Board was concerned to note Galderma's submission that the meeting had been organised by a sole key account manager (KAM) at short notice acting on his/her own without Galderma's knowledge; this information had not been submitted to the Panel and, that very little detail had been provided in Galderma's appeal. The Appeal Board was not convinced that the KAM was the only person who knew about the meeting; it noted Galderma's submission that six other Galderma staff were at the meeting; the employee who had presented on Pliaglis and five other sales staff. The Appeal Board queried how a single KAM was able to cooperate with a nurse support group, agree a product discount, book national and international speakers, generate meeting materials, source and fund the venue etc without a more senior member of staff having to formally agree and approve the arrangements.

The Appeal Board was extremely concerned about the overall arrangements for the meeting and the lack of control. It noted that the presentations had not been certified and there were no speaker agreements or contracts. The Appeal Board was extremely concerned that the presentation on botulinum toxins by a Galderma employee, discussed the use of botulinum toxin in a number of unlicensed indications. This was totally unacceptable and contrary to the Code.

The Appeal Board considered that the overall arrangements were such that Galderma had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel's ruling of a breach of Clause 2 was upheld. The appeal was thus unsuccessful.

In relation to the report from the Panel, the Appeal Board noted the rulings of breaches of the Code. The Appeal Board was appalled and extremely concerned about the materials and arrangements for the meeting; there had been astonishing failures at all levels.

The Appeal Board queried why the submission that a lone KAM, acting contrary to company policy, was responsible for the issues in this case, had only appeared as a brief statement in the appeal and not in the various responses to the Panel, especially considering the number of times the Panel had had to ask Galderma for information. Notwithstanding the KAM's apparent disregard for company policies, Galderma was still responsible for his/her actions under the Code. The Appeal Board questioned Galderma's care and attention taken in its responses to the Panel and its appeal in this case. External confidence in self regulation relied upon a full and frank disclosure at the outset. This and the circumstances of the meeting implied a fundamental lack of understanding of the requirements of the Code and a lack of control exhibited by Galderma. The Appeal Board queried how seriously Galderma took its corporate responsibilities under the Code.

The Appeal Board was extremely concerned about Galderma's conduct, and having considered all the sanctions available under Paragraph 11.3 of the Constitution and Procedure decided that the company should be publicly reprimanded.

The Appeal Board also decided to require an audit of Galderma's procedures in relation to the Code to be carried out as soon as possible and at the same time as that in Case AUTH/2684/12/13. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary. Following notification of the Appeal Board's consideration, Galderma agreed a date for the audit but after receiving the detailed reasons it then declined to be audited or sign the undertaking and assurance related to the Appeal Board ruling and informed the Authority that it no longer accepted the jurisdiction of the PMCPA. This prompted a second report to the Appeal Board.

The Appeal Board noted that by failing to provide the requisite undertaking and assurance and declining the audit Galderma had failed to comply with the procedures set out in Paragraph 10 of the Constitution and Procedure and thus the Appeal Board decided, in accordance with Paragraph 11.4, to remove Galderma from the list of non member companies which had agreed to comply with the Code. Thus responsibility for Galderma under the Code could no longer be accepted. The Medicines and Healthcare Products Regulatory Agency (MHRA) and the ABPI Board of Management were subsequently advised of the Appeal Board's decision.

An anonymous, non-contactable complainant who described him/herself as a registered nurse complained about arrangements for an aesthetics meeting organised by Galderma (UK) Limited. The meeting in question was an educational day in association with a nurse support group. The complainant provided the agenda which listed four presentations, two of which were particularly relevant to medicines marketed by Galderma; one was about botulinum toxins (Galderma

marketed Azzalure) and the second was about the company's product Pliaglis (tetracaine/lidocaine), a topical anaesthetic for use in dermatological procedures. The covering letter sent with the agenda stated that there was no meeting charge for members of the nurse support group but 'due to the high calibre of the speakers provided by Galderma you are required to have purchased a minimum of Two Emervel Classics from [named pharmacy] between now and the 16th November 2013'.

COMPLAINT

The complainant wrote as he/she was a member of the nurse support group, which recently held an event fully sponsored by Galderma.

The complainant had been in the cosmetic/aesthetic industry for many years and noted that the industry often received bad press, often unfairly. The complainant always looked to raise standards, hence the reason he/she was a member of this group amongst others. One way of raising standards was to increase education and this was something he/she strived to do. The complainant stated that he/she had particularly wanted to go to the meeting and was particularly interested in the presentation on botulinum toxin in aesthetics.

The complainant was disgusted, however, that he/she was forced to buy at least two boxes of Galderma's dermal fillers to be able to attend. The complainant referred to the invitation which stated:

> 'For all current members there is no charge for the conference HOWEVER due to the high calibre of the speakers provided by Galderma you are required to have purchased a minimum of Two Emervel Classics from [named pharmacy] between now and the 16th November 2013.'

The complainant submitted that firstly that was just wrong and, secondly, he/she did not like or use the particular filler, and thirdly was not even trained on it. The complainant noted that the two boxes that he/she had been forced to buy in order to improve his/her education were now sat on a shelf.

The complainant submitted that these types of actions did not do the industry any favours and just lowered standards, which was exactly the opposite of what he/she hoped to achieve.

When writing to Galderma, the Authority asked it to consider the requirements of Clauses 2, 9.1 and 18.1.

RESPONSE

Galderma submitted that Emervel was a medical device. As the complaint concerned the purchase of a medical device in relation to attendance at an educational event related to medical devices the company considered that the arrangements relating to this regional educational meeting fell outside the scope of the Code and trusted that the matter could be closed.

In response to a request from the case preparation manager to respond to the complaint, Galderma submitted that the nurse support group approached a key account manager (KAM) with a proposal to organise and support a regional product educational/training day. The nurse support group negotiated this type of event with manufacturers and suppliers in order to offer its membership on a frequent basis. The subject of the event, Restylane Skin Boosters (a medical device marketed by Galderma), was proposed by the nurse support group together with some suggestions for potential speakers. Galderma agreed to source and fund a suitable venue, contact and fund the speakers, and provide some general support for the organisation of the day. The nurse support group also asked a supplier of medical aesthetic equipment and a wholesaler of aesthetic products to sponsor the event; one of these funded the lunch/refreshments and provided support for the day and the other offered a discount on the supply of product as part of the registration package and provided support for the day including checking the professional status of the attendees.

The KAM considered that the meeting fell outside of the Code as it related to Galderma's medical device products and therefore went ahead with the arrangements. The nurse support group had proposed a number of topics and potential speakers that would benefit its membership. The KAM contacted the two speakers proposed by the nurse support group and a third speaker to cover the other topics proposed by the nurse support group. During the discussions, the nurse support group proposed to additionally include a presentation on Pliaglis on the agenda as it thought it would benefit its membership. The KAM included this in the final agenda and arranged with a Galderma employee to do a short presentation.

The KAM prepared a 'save the date' flyer which was emailed to the nurse support group to distribute to its membership. A final agenda was prepared and emailed to the nurse support group for distribution to its members.

The nurse support group was responsible for drafting the covering letters/emails and distributing these together with the invites to its members.

The named pharmacy monitored the registration desk on the day of the meeting and had since provided a list of 39 attendees. Galderma did not know how many units of Emervel Classic were purchased as this was done directly with the named pharmacy. A list of the items Galderma made available to delegates as part of the meeting were provided.

Galderma stated that it did not have access to any of the presentations other than the one about Pliaglis. Should copies of the other presentations be required, Galderma could request copies from the presenters.

Galderma stated that there was no contract between it and the other co-sponsors or any written agreement between it and the nurse support group. All discussions were done during face-to-face meetings. There were also no written agreements between Galderma and the speakers.

Galderma explained that it was not uncommon within the aesthetics industry for delegates to be

required to purchase product before attending product educational/training sessions. As the complaint specifically concerned the purchase of a medical device in relation to attendance at an event focussed on medical devices, Galderma submitted that the activity neither breached Clauses 2, 18.1 or 19.1 of the Code nor fell within the scope of the Code.

In response to a request from the Panel for further information, Galderma provided copies of the presentations and submitted that all discussions and agreements between the KAM and the speakers were carried out verbally; there was no supporting documentation. Galderma clarified that its general support for the organisation of the day included creating the 'save the date' flyer and the 'final agenda', copies of which had been provided. The artwork for these documents was created internally at the request of the KAM. The documents were provided as PDFs to the nurse support group for approval and subsequent distribution to its members. Additionally, Galderma staff were present at the venue to ensure that delegates were directed to the appropriate rooms.

Galderma submitted that all attendees had to purchase Emervel before the event. The named pharmacy was responsible for this element and for monitoring the registration desk. The named pharmacy was not willing to share the purchasing details of attendees with Galderma and so it could not confirm if anyone attended without having purchased Emervel.

Galderma created the artwork for both the flyer and the agenda and therefore had seen them prior to their distribution. Galderma had not prepared the emails sent by the nurse support group nor did it know how many emails the nurse support group had sent. However, Galderma saw some of the emails that the nurse support group had sent to its membership in connection with this meeting.

Seven Galderma staff were at the meeting including the product manager who presented on Pliaglis, the KAM who coordinated the meeting and five other sales staff. Galderma did not have a stand at the meeting although Restylane and Emervel banners were displayed in the room.

PANEL RULING

The Panel disagreed with Galderma's submission that as the complaint specifically concerned the 'purchase of a medical device' in relation to attendance at an event which focused on medical devices it did not fall within the scope of the Code. The Panel noted that the Code applied, *inter alia*, to the promotion of medicines to health professionals and appropriate administrative staff, Clause 1.1 referred. It did not apply to the promotion of devices *per se* unless such devices could only be used with specific medicines. Galderma marketed Azzalure (botulinum toxin) and Pliaglis (tetracaine/lidocaine). The Panel noted that the agenda included a presentation on botulinum toxins in aesthetics which compared Azzalure, Dysport, Botox, Vistabel, Xeomin and Bocouture and a presentation on Pliaglis by Galderma's product manager. A Pliaglis leavepiece was also available. In addition, the Panel noted that the agenda stated that the meeting provided 'an opportunity to present evidence in your prescribing portfolio relating to Toxin'. The Panel considered that the meeting clearly promoted Galderma's prescription only medicines and in this regard noted that the complainant had attended because he/she was particularly interested in the presentation on botulinum toxins.

The Panel noted the nurse support group's role in relation to the meeting. The Panel noted that Galderma's role included contacting and verbally finalising arrangements and paying the speakers, two of whom were suggested by the nurse support group including a consultant oculoplastic surgeon and a senior aesthetic product developer with Galderma. Galderma provided an additional internal speaker, sourced and funded the venue, drafted and provided the flyer and agenda to the nurse support group for distribution and provided general support. The covering email to the agenda, drafted by the nurse support group described the event as a 'Galderma educational day'. Seven Galderma staff attended including five sales staff. The Panel considered that given Galderma's role and the content of the meeting, the matter of complaint came within the scope of the Code.

Whilst noting that elements of the meeting referred to medical devices, the Panel considered that the content in relation to prescription only medicines and the overall meeting arrangements had to comply with the Code. This would include the requirement for delegates to purchase a product before attending. If the meeting content was only about medical devices then it was likely that the Code would not apply.

The Panel noted that Clause 18.1 stated that no gift, pecuniary advantage or benefit might be supplied, offered or promised to members of the health professions or to administrative staff in connection with the promotion of medicines or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clauses 18.2 and 18.3. Delegates could not be paid to attend meetings unless the arrangements were bona fide fees for services. The Code also prohibited the payment (or offer) of a fee for the grant of an interview (Clause 15.3).

The Panel noted that the email sent with the agenda stated that there was no charge for the meeting for nurse support group members but 'due to the high calibre of the speakers provided by Galderma you are required to have purchased a minimum of Two Emervel Classics from [named pharmacy] between now and the 16th November 2013'. The covering letter further stated that '[named pharmacy] have kindly confirmed a special offer price for us all of £74.34 per box. You will also receive a free Restylane Skin Booster and complimentaries on the day. For a cost of £150 we get a fabulous deal, equivalent to £240 worth of products plus the meeting'. Delegates had to bring their invoices to the conference as proof of purchase to gain entry. Those who were not members of the nurse support group were charged £40 to attend and were also required to purchase 2 packs of Emervel Classic. The Panel noted Galderma's submission that it was not uncommon within the aesthetics industry for there to be a requirement to purchase a product before attending educational or training sessions.

The Panel noted its finding above that the overall arrangements had to comply with the Code. It could also be argued that attendees were paid £90 to listen to talks promoting medicines. The Panel noted the requirements of Clause 18.1. The Panel considered that the discount offered on the obligatory purchase of Emervel together with the items received on the day meant that attendees were given a pecuniary advantage of a minimum of £90 in connection with the promotion of Azzalure and Pliaglis and a breach of Clause 18.1 was ruled. That nurse support group members did not otherwise pay to attend the meeting and non members did was, in the Panel's view, irrelevant.

The Panel noted Galderma's submission that it was not uncommon within the aesthetics industry for there to be a requirement to purchase a product before attending product educational/training sessions. The Panel noted its comments above in this regard. The Panel noted that no training on Emervel Classic was provided at the meeting. The Panel considered that patient safety was extremely important. The Panel considered that requiring a health professional to purchase a product that he/she knew nothing about and upon which he/she was not trained raised possible patient safety concerns. In addition paying health professionals to attend promotional meetings was unacceptable. The Panel considered that overall high standards had not been maintained and a breach of Clause 9.1 was ruled. In addition the Panel considered that the circumstances were such that Galderma had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

During its consideration of this case the Panel was concerned about a number of matters which, in its view, demonstrated that Galderma had a very poor knowledge of the requirements of the Code and/or a reckless attitude towards its application. The Panel noted its findings and rulings as set out above. In addition, the Panel was very concerned that the presentation on botulinum toxins by Galderma's product developer discussed the use of botulinum toxin in a number of unlicensed indications including depression, rosacea and reduction in sweating. The Panel considered that the promotion of unlicensed indications was a very serious matter contrary to Clause 3.2. To compound matters the presentation did not appear to have been certified by the company contrary to Clause 14.1.

The Panel was also concerned about the lack of formality and clear written agreements in relation to the meeting. The Panel was further concerned that there were no contracts in place between Galderma and its speakers (Clause 20.1) nor were there any briefing documents setting out the requirements of the Code in relation to these speakers.

The Panel was further concerned about the documentation provided to delegates about the meeting. Neither the agenda nor its covering email incorporated the Pliaglis and Azzalure prescribing information (Clause 4.1). Whilst the 'save the date' flyer and the agenda featured Galderma's corporate logo, neither made the extent and nature of the company's involvement sufficiently clear and each was inconsistent with the covering email to the agenda which described the event as Galderma's meeting (Clause 19.4).

The Panel considered Galderma's conduct in this case warranted consideration by the Code of Practice Appeal Board and decided to report the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for it to consider whether further sanctions were warranted.

APPEAL BY GALDERMA

Galderma submitted that a breach of Clause 2 was inappropriate; it strongly refuted the argument that the complainant could be exposed from a safety perspective through not being able to attend the event. The techniques for administering all major hyaluronic acid products were standardised and would be covered in an equivalent way by any company's training. It was therefore inappropriate to suggest that this amounted to 'requiring a health professional to purchase a product he/she knew nothing about'.

Similarly, Galderma noted that its entire role in relation to the meeting was a result of the nurse support group requesting sponsorship/support and due to short time lines on this occasion one KAM acted contrary to company policy. Galderma submitted that these actions did not reflect the attitude or procedures of the company as a whole.

Galderma submitted that if the breach of Clause 2 was ruled on safety grounds this was based on a misunderstanding of the practice of this sector of the medical devices market. If the breach was based on Galderma's procedures it noted that this involvement was unauthorised by the company and once discovered appropriate action was taken. In this regard Galderma further refuted the suggestions that it had 'poor knowledge' of, or a 'reckless attitude' towards the Code and referred to its past unblemished record in relation to the Code and its prompt responses to each of the PMCPA's questions in this matter.

APPEAL BOARD RULING

The Appeal Board noted that contrary to Galderma's appeal submission the Panel's ruling of a breach of Clause 2 was not limited to matters of patient safety. The ruling referred to all the circumstances of the case.

The Appeal Board was not clear what was meant by Galderma's appeal that it refuted the argument that 'the complainant could be exposed from a safety perspective through not being able to attend the [nurse support group] event'. The Galderma representative acknowledged that this was badly worded and in explanation referred to the similarity of the injection technique for all dermal fillers. In Galderma's view as long as a health professional knew the general technique, not being trained to administer a specific dermal filler did not have adverse implications for patient safety and thus the Panel's ruling of a breach of Clause 2 in this regard was based on a misunderstanding.

In response to a question regarding what was meant by Galderma's appeal that '… this involvement was

unauthorized by the company …', the Galderma representative stated that the meeting had been organised by a sole KAM at short notice acting on his/her own without Galderma's knowledge. The Appeal Board was very concerned that this information had not been submitted in any of Galderma's responses to the Panel and that very little detail was provided in Galderma's appeal. The Appeal Board was not convinced that the KAM was the only person who knew about the meeting; it noted Galderma's submission that in addition to the KAM, six other Galderma staff were at the meeting including the product manager who had presented on Pliaglis and five other sales staff. At the very least the product manager would also have been aware of and involved with the meeting. The Appeal Board queried how a single KAM was able to cooperate with a nurse support group, agree a product discount, book national and international speakers, generate meeting materials, source and fund the venue etc without a more senior member of staff having to formally agree and approve the arrangements.

The Appeal Board was extremely concerned about the overall arrangements for the meeting and the lack of control. It noted that the presentation slides had not been certified and there were no speaker agreements or contracts despite the fact that, according to the Galderma representative, the company had previously engaged the speakers and provided them with briefings and contracts. The Appeal Board was extremely concerned that the presentation on botulinum toxins by the person who worked for Galderma, discussed the use of botulinum toxin in a number of unlicensed indications. This was totally unacceptable and contrary to the Code.

The Appeal Board noted that Galderma had accepted the Panel's ruling of a breach of Clause 18.1 in that attendees were given a pecuniary advantage in connection with the promotion of Azzalure and Pliaglis. Galderma had also accepted the Panel's ruling of a breach of Clause 9.1 for failing to maintain high standards.

The Appeal Board noted its comments above and considered that the overall arrangements were such that Galderma had brought discredit upon and reduced confidence in the pharmaceutical industry. Consequently the Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal was unsuccessful.

COMMENTS FORM GALDERMA ON THE REPORT

At the consideration of the report, the Galderma representative apologised on behalf of the company for the mistakes it had made. The KAM responsible for the meeting had been reprimanded and training on the Code for all staff was underway.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted the rulings of breaches of the Code. The Appeal Board was appalled and extremely concerned about the materials and arrangements for the meeting. In its view, there were astonishing failures at all levels.

The Appeal Board queried why the submission that a lone KAM, acting contrary to company policy, was responsible for the issues in this case, had only appeared as a brief statement in the appeal and not in the various responses to the Panel, especially considering the number of times the Panel had had to ask Galderma for information. Notwithstanding the KAM's apparent disregard for company policies, Galderma was still responsible for his/her actions under the Code. The Appeal Board questioned Galderma's care and attention taken in its responses to the Panel and its appeal in this case. External confidence in self regulation relied upon a full and frank disclosure at the outset. This and the circumstances of the meeting implied a fundamental lack of understanding of the requirements of the Code and a lack of control exhibited by Galderma. The Appeal Board queried how seriously Galderma took its corporate responsibilities under the Code.

The Appeal Board was extremely concerned about Galderma's conduct, and having considered all the sanctions available under Paragraph 11.3 of the Constitution and Procedure decided that the company should be publicly reprimanded.

The Appeal Board also decided that an audit of Galderma's procedures in relation to the Code should be carried out as soon as possible and at the same time as the audit required in Case AUTH/2684/12/13. The KAM who Galderma submitted organised the meeting at issue, together with his/her manager should be interviewed during the audit. On receipt of the audit report the Appeal Board would consider whether further sanctions including a report to the ABPI Board of Management were necessary.

* * * * *

Following notification of the Appeal Board's consideration, Galderma agreed a date for the audit but after receiving the detailed reasons it then in Case AUTH/2684/12/13 declined to be audited or sign the requisite undertaking and assurance related to the Appeal Board rulings and it informed the Authority that it no longer accepted the jurisdiction of the PMCPA. Galderma had also strongly considered that the Panel and the Appeal Board had not given it a fair hearing on this matter.

The Director asked Galderma to clarify its position in relation to Case AUTH/2685/12/13 and to provide further details as to why it considered that the Panel and the Appeal Board had not given it a fair hearing on this matter.

COMMENTS FROM GALDERMA

Galderma submitted that with regard to the fairness of Galderma's hearing, the company did not see any benefit in reiterating its previous arguments in the light of its decision to resign from the jurisdiction of the PMCPA.

Galderma confirmed that as it had resigned from the jurisdiction of the PMCPA, it would not undergo an audit with respect to Case AUTH/2685/12/13. As stated in Case AUTH/2684/12/13 Galderma was fully prepared to undergo an audit by the MHRA as a possible consequence.

In the light of its resignation from the PMCPA's jurisdiction, Galderma knew of, and was comfortable with the Appeal Board's right under the provisions of Paragraph 11.4 of the Constitution and Procedure to remove the company from the list of non member companies which had agreed to comply with the Code and advise the MHRA that responsibility for Galderma under the Code could no longer be accepted. Galderma further noted that such action was required in accordance with the 3 November 2005 Memorandum of Understanding between the ABPI, PMCPA and MHRA. Galderma acknowledged the PMCPA's obligation to notify the ABPI Board of Management that such action had been taken.

* * * * *

In accordance with Paragraph 11.1 of the Constitution and Procedure the Authority reported Galderma to the Code of Practice Appeal Board for it to decide whether to remove the company from the list of non member companies which had agreed to comply with the Code and advise the Medicines and Healthcare Products Regulatory Agency (MHRA) that responsibility for Galderma under the Code could no longer be accepted. (Paragraph 11.4 of the Constitution and Procedure).

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APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE AUTHORITY

The Appeal Board noted that Galderma had asked to be removed from the list of non member companies that had agreed to comply with the Code.

The Appeal Board noted that the Director had asked Galderma for further details as to why it considered that the '… Panel and Appeal Board have failed to give Galderma a fair hearing on this matter…'. The Appeal Board considered this was a very serious allegation, particularly as the PMCPA had followed its Constitution and Procedure in dealing with these cases. Galderma had not provided further detail.

The Appeal Board noted that by failing to provide the requisite undertaking and assurance and declining the audit Galderma had failed to comply with the procedures set out in Paragraph 10 of the Constitution and Procedure and thus the Appeal Board decided, in accordance with Paragraph 11.4, to remove Galderma from the list of non member companies which had agreed to comply with the Code. Thus responsibility for Galderma under the Code could no longer be accepted. The MHRA and ABPI Board of Management were subsequently advised of the Appeal Board's decision.

Complaint received	**12 December 2013**
Undertaking for matters not appealed	**6 May 2014**
Appeal considered	**15 May 2014**
Report to Appeal Board	**15 May 2014, 24 July 2014**
MHRA informed	**4 August 2014**
ABPI Board informed	**4 August 2014**

CASE AUTH/2694/1/14

ANONYMOUS v PHARMACOSMOS

Promotion of Monofer

An anonymous contactable complainant complained about the advertising of Monofer (iron (III) isomaltoside 1000), by Pharmacosmos UK on two of its linked websites.

The complainant explained that when using the Pharmacosmos website to review two intravenous (IV) iron products he/she noted that the triangle denoting additional monitoring was blue rather than black. The complainant followed the link from the Pharmacosmos website to www.monofer.com. The complainant stated that although it was described as an international site it was linked from the UK website and had a black triangle which indicated that the site was aimed at the UK. Although browsers had to state that they were a health professional, the website stated that 'This medical website focuses on Monofer (iron isomaltoside 1000), a treatment for iron deficiency anemia'. Most other sites did not specify the medicines' uses before visitors had indicated whether they were health professionals. The complainant submitted that a lot of the health professional site was visible behind the initial box and could easily be seen by the general public. The complainant alleged that the summary of product characteristics (SPC) on the website was out of date and alleged that if it was used patients could potentially be discharged without monitoring for 30 minutes and the medicine could be used in contraindicated patients. The Monofer website described the iron matrix technology as new which was not so; Monofer had been available for several years.

The detailed response from Pharmacosmos is given below.

The Panel noted that the Code stated that when required by the licensing authority, all promotional material must show an inverted black triangle to denote that special reporting was required in relation to adverse reactions. The Panel noted Pharmacosmos' submission that the publicly visible UK corporate website was non-promotional in nature. It also considered that Pharmacosmos had changed the relevant part of the website so that the triangle was now black. The Panel noted that the Code only required a black triangle to be included on promotional material and considered that the complainant had not proved his/her complaint on the balance of probabilities that the website was promotional and thus no breach of the Code was ruled.

The Panel noted that the www.monofer.com website was described by Pharmacosmos UK as the international website, however the SPC page appeared to feature the UK prescribing information as the NHS cost was given in £ sterling. This page also referred to www.mhra.gov.uk/yellowcard for reporting side effects in the UK. The prescribing information and monitoring details were not provided for any other country. The Panel noted that the website specifically referred to the availability or use of Monofer in the UK which was one of the factors listed in the Code as bringing such material placed on the internet by a UK company or its affiliate within the scope of the Code. In addition the site was linked from the Pharmacosmos UK website. The Panel considered that although the website stated that 'Monofer.com is a resource for healthcare professionals outside US only. The information on this site is not country-specific and may contain product information otherwise not accessible or valid in your country', the emphasis on the UK was such that on balance the UK Code applied.

The Panel noted that when entering the www.monofer.com site, a pop-up window appeared which stated 'Welcome to Pharmacosmos' international Monofer website. This medical website focuses om [sic] Monofer (iron isomaltoside 1000), a treatment for iron deficiency anemia'. The health professional site was visible behind the pop-up window. The Panel noted from the screenshot that the phrases: 'High dose Infusi', 'up to 20', and 'High dose iron' were visible and part of the letters that formed the words 'in just one visit' were visible on a photograph showing a hand holding a vial of Monofer. Overall, the Panel considered that the claim 'High dose iron in just one visit' was readable. The next question to consider was whether the visible claims promoted Monofer or whether the page at issue was in line with the Code.

The Panel noted Pharmacosmos' submission that readers accessed the site because they were already seeking information regarding Monofer. The Panel noted that members of the public would be able to access the Monofer SPC on the eMC which would include the product's indication. The Code made it clear that a number of materials including the SPC could be made available as a resource for the public/patients. The Panel considered that the pop-up window in combination with promotional claims for Monofer intended for health professionals which were visible to members of the public meant that a prescription only medicine had been promoted to the public who would also be encouraged to ask their health professionals to prescribe it and breaches of the Code were ruled. The Panel considered that high standards had not been maintained. A breach of the Code was ruled.

The complainant alleged that the Monofer SPC on the website was out of date. The Panel noted Pharmacosmos' submission that after the European Medicines Agency had reviewed all IV iron products in September 2013, an update of all the SPCs was

recommended. The Panel noted Pharmacosmos' submission that the updated Monofer SPC was currently under review by the regulatory authorities and, as yet, no formal changes had been approved. Pharmacosmos also submitted that the SPC on Monofer.com was the current version. The Panel did not consider that the complainant had established that the Monofer SPC on the website was out of date. Thus the Panel ruled no breaches of the Code including no breach of Clause 2.

The Panel noted Pharmacosmos' submission that that the word 'new' should no longer have appeared as Monofer had been available for several years. A breach of the Code was ruled as acknowledged by the company.

Prior to being advised of the Panel's rulings, Pharmacosmos indicated that it no longer wished to accept the jurisdiction of the Authority and did not complete and return the form of undertaking and assurance. The Authority was bound by Paragraph 11.4 of the Constitution and Procedure to report the company to the Code of Practice Appeal Board.

In relation to the report from the Authority the Appeal Board noted that Pharmacosmos A/S had previously agreed to abide by the Code as a non member company. The complaint in this case was the first one which involved Pharmacosmos UK so that company had been invited to join the list of non member companies that agreed to comply with the Code and accept the jurisdiction of the PMCPA.

The Appeal Board noted the reasons given by Pharmacosmos for its decision not to join the list of non member companies that had agreed to comply with the Code and accept the jurisdiction of the PMCPA.

The Appeal Board noted Pharmacosmos' submission that it had changed the material at issue. However, the Appeal Board noted that by failing to provide the requisite undertaking and assurance Pharmacosmos had failed to comply with the procedure set out in Paragraph 7 of the Constitution and Procedure and thus the Appeal Board decided, in accordance with Paragraph 11.4 of the Constitution and Procedure, to remove Pharmacosmos from the list of non member companies which had agreed to comply with the Code*. Responsibility for Pharmacosmos under the Code could no longer be accepted. The Medicines and Healthcare Products Regulatory Agency (MHRA) and the ABPI Board of Management were subsequently advised of the Appeal Board's decision.

****Pharmacosmos UK submitted that it could not be removed from the non-members list as it had never formally agreed to join it. Pharmacosmos A/S and Pharmacosmos UK had, however, between 2010 and April 2014, each demonstrated their willingness to voluntarily comply with the Code and accept the jurisdiction of the Authority both in terms of complaints received and complaints submitted and in that regard both appeared to consider themselves effectively, if not formally, on the non members list.***

An anonymous, contactable complainant complained about the advertising of Monofer (iron (III) isomaltoside 1000), by Pharmacosmos UK Ltd on its website (www.pharmacosmos.co.uk).

Monofer was indicated for the treatment of iron deficiency anaemia when oral iron preparations were ineffective or could not be used and where there was a clinical need to deliver iron rapidly

COMPLAINT

The complainant referred to two linked websites. The complainant explained that he/she used www.pharmacosmos.co.uk to review Pharmacosmos' two intravenous (IV) iron products. The complainant assumed that black triangles needed to be black and noted that the one here was blue. The complainant followed the link from the Pharmacosmos website to the www.monofer.com site. The complainant stated that he/she had previously visited this site and although it described itself as an international site it was linked from the UK website so appeared to be intended for his/her viewing. The complainant noted that Monofer had a black triangle and had had this for some time prior to all IV irons requiring one in Europe which indicated that the site was aimed at the UK. Although browsers had to state that they were a health professional, the website stated that 'This medical website focuses on Monofer (iron isomaltoside 1000), a treatment for iron deficiency anemia'. Most other sites the complainant had used did not specify the medicines' uses before visitors had indicated whether they were health professionals. The complainant submitted that a lot of the health professional site was visible behind the initial box, something that could easily be seen by the general public. The complainant was most concerned that the summary of product characteristics (SPC) on the website was out of date which was concerning as the European Medicines Agency (EMA) / Medicines Healthcare Products Regulatory Agency (MHRA) had raised concerns over IV irons safety last year. The complainant alleged that if this SPC was used patients would potentially be discharged without monitoring for 30 minutes and Monofer could be used in contraindicated patients. The Monofer website described the iron matrix technology as new which was not so; Monofer had been available for several years.

When writing to Pharmacosmos, the Authority asked it to respond in relation to Clauses 2, 4.11, 7.2, 7.11, 9.1, 23.1 and 23.2 of the Code. It appeared that the case preparation manager was referring to the 2014 Code.

RESPONSE

Pharmacosmos submitted that it was fully committed to compliance with the Code and welcomed the opportunity to comment on the concerns raised by the complainant. As part of its investigation, it undertook a thorough review of the Pharmacosmos websites. Pharmacosmos addressed each point in turn.

Pharmacosmos submitted that www.pharmacosmos.co.uk was the publicly visible UK corporate

website. It was non-promotional and intended as a public 'face' for the company in the manner of a typical company website. The site included a link to a section which listed the products that Pharmacosmos made available in the UK.

Within this section, the company decided to include the black triangle symbol even though there was no requirement under the Code for it to do so. The website was non-promotional in nature and acted as a window to the corporate aspects of its business, including providing contact information.

As the complainant correctly highlighted, the standard colour for the black triangle should, indeed be black. The text used in this area of the website was a very dark blue. This was an oversight; Pharmacosmos was grateful to the complainant for pointing this out and it had changed the colour of the triangle to black.

However, Pharmacosmos denied a breach of Clause 4.11 as that aspect of the Code related specifically to the presence of the triangle on promotional material. The section of the website referred to by the complainant was not promotional (by virtue of the fact it was intended for public viewing) and therefore the colour of the triangle was not subject to the specific clause. While Pharmacosmos recognized that it was a fine point, it was, nevertheless an important distinction.

As stated in the complainant's letter, www.monofer.com could be accessed via a link from the pharmacosmos.co.uk site. Pharmacosmos submitted that it could be seen from a screenshot provided that the source page on pharmcosmos.co.uk clearly indicated that the products were for health professionals. A link allowed the reader to visit monofer.com. Access was also provided to the eMC website.

On first reaching monofer.com, the reader was presented with a pop-up window that asked the reader to click to indicate the most relevant area of the site for them: health professional or public. This pop-up window to Monofer.com as stated by the complainant included the indication for Monofer. The intention of this pop-up was to explain briefly the purpose of the site so that the user could select the most appropriate route of entry (health professional/public).

Pharmacosmos submitted that it was appropriate for readers to understand the purpose of the site before they selected a route of entry so they could be sure what the correct action was for them to take. This was an informative message presented in response to the user accessing a medicine-specific website. Pharmacosmos was not aware of any ban on stating the indication, *per se*, in this context and accordingly denied a breach of Clauses 23.1 and 23.2.

Pharmacosmos reviewed the pop-up window again in light of the complainant's comments. The window background was transparent. Pharmacosmos agreed that some of the background screen was therefore visible, albeit much less prominently than the pop-up itself, as could be seen from the screen shot provided.

Pharmacosmos submitted that it had already taken steps to amend the construct of the website such that users now entered a totally separate landing page before being redirected to the appropriate area of the website. A copy of the revised screenshot was provided.

Pharmacosmos provided a screenshot that accurately showed the visible text and submitted that complete phrases were *not* visible.

Specifically the phrases: 'High dose Infusi' 'up to 20', and 'High dose iron' and the top third of the letters that formed the words 'in just one visit ' were readable on a photograph showing a hand holding a vial of Monofer.

Whilst there was no intention to advertise medicines to the public, Pharmacosmos accepted that these statements and the photograph together could be regarded as communicating limited product information to the public.

However, Pharmacosmos did not consider that the visible wording (primarily 'high dose iron') constituted any form of benefit that would be relevant to the patient. It merely reflected the actual licensed indication. As such Pharmacosmos did not consider this should constitute advertising to the public and denied a breach of Clauses 23.1 and 23.2.

Pharmacosmos asked the PMCPA to bear in mind that readers accessed the site because they were already seeking information regarding Monofer. In that respect, there was no intention that the visible statements should encourage members of the public to ask their health professional to prescribe Monofer. The visible information was factual and presented in a balanced way; it needed to be in order to comply with the health professional aspects of the Code. It was not misleading regarding safety as no safety claims were made. The statements did not raise unfounded hopes of successful treatment, not least because the only visible statements were in respect of dosage (high dose), not outcome. The other statement that was not fully readable concerned convenience (one visit) but the average reader would have to study the text to even work out what the phrase was because approximately only the top third of the letters in the words were visible.

Clause 9.1 related to the maintenance of high standards. Pharmacosmos acknowledged that some aspects of the site were visible behind the pop-up, however there was clearly no intention to promote; the pop-up box was designed to direct readers to the appropriate area of the website. On selecting 'patient or relative', readers were shown the non-promotional area of the website that had been specifically designed for access by the public. The monofer.com link was accessible from the product page on the corporate website; this page clearly indicated that the products were for use by health professionals and readers were required to confirm their status as a health professional before they directly accessed the health professional area of the site.

Pharmacosmos had already taken steps to amend the construct of the website such that the user now

entered a totally separate landing page before being redirected to the appropriate area of the website.

Whilst one promotional area of the health professional text was indeed visible, there was no visibility of a complete claim. The average reader was unlikely to even take notice of the background as the focus would be on the pop-up, which automatically appeared. Pharmacosmos did not consider that this constituted a failure to maintain high standards as alleged.

Pharmacosmos submitted that it acted quickly to address the concerns raised and wished to reassure the PMCPA of its best intentions in this and all matters of compliance. Pharmacosmos had immediately undertaken discussions with its international business and the website was corrected immediately. Accordingly, it denied a breach of Clause 9.1.

Pharmacosmos submitted that the SPC as listed on the website was correct and current.

After a review of all intravenous (IV) iron products in Europe by the EMA in Septemebr 2013, an update of the SPC for all IV irons was recommended. Many of the intended changes to the SPC had been the subject of public discussions. The update of the Monofer SPC was currently under review by the regulatory authorities and, as yet, no formal changes had been approved. Therefore the SPC displayed on Monofer.com was the correct version. When it was approved, the SPC on the website would be changed.

Accordingly Pharmacosmos denied breaches of Clauses 7.2, 9.1 and 2.

Having reviewed the page identified by the complaint and the entire Monofer.com website, Pharmacosmos was able to find only a single use of the word 'new' at the very foot of the page:

> 'Based on Pharmacosmos' new iron Matrix technology, Monofer is the only treatment for iron deficiency anaemia that combines the advantages of 1) a dose range up to 20mg/kg with no upper dose limit, 2) a fast high dose iron correction in one visit, and 3) no test dose requirement'.

Pharmacosmos accepted that the word 'new' should no longer appear; it had been removed from the website, but accordingly, Pharmacosmos acknowledged a breach of Clause 7.11. A screenshot of the revised website was provided.

PANEL RULING

The Panel noted the clauses of the 2014 Code cited by the case preparation manager. The transition period for newly introduced requirements applied from 1 January 2014 until 30 April 2014. There had been no changes to Clauses 2, 4.11, 7.2 and 9.1. Clause 23.1 and 23.2 had been renumbered (previously Clauses 22.1 and Clause 23.2). Thus the Panel decided to use the 2014 edition as in relation to the complaint being considered; the relevant requirements were the same as in the Second 2012 Edition (as amended).

The Panel noted that Clause 4.11 of the Code stated that when required by the licensing authority, all promotional material must show an inverted black triangle to denote that special reporting was required in relation to adverse reactions. The Panel noted Pharmacosmos' submission that the website, www.pharmacosmos.co.uk, was the publicly visible UK corporate website and was non-promotional. It also considered that Pharmacosmos had changed the relevant part of the website so that the black triangle was now black. The Panel noted that Clause 4.11 only required a black triangle to be included on promotional material and considered that the complainant had not proved his/her complaint on the balance of probabilities that the website was promotional and thus no breach of Clause 4.11 of the Code was ruled. During its consideration of this matter, the Panel noted that the 2014 Code included new requirements about the use of the black triangle in materials for patients, Clause 23.3. It requested that this was drawn to the attention of Pharmacosmos.

The Panel noted that the website www.monofer.com was described by Pharmacosmos UK as the international Monofer website, however the SPC page appeared to feature the UK prescribing information as the NHS cost was given in £ sterling. This page also referred to www.mhra.gov.uk/yellowcard for how to report side effects in the UK. The prescribing information and monitoring details were not provided for any other country. The Panel noted that the website made specific reference to the availability or use of the medicine in the UK which was one of the factors listed in Clause 25.2 as bringing such material placed on the internet by a UK company or its affiliate within the scope of the Code. In addition the site was linked from the Pharmacosmos UK website. The Panel considered that although the website stated that 'Monofer.com is a resource for healthcare professionals outside US only. The information on this site is not country-specific and may contain product information otherwise not accessible or valid in your country', the emphasis on the UK was such that on balance the UK Code applied.

The Panel noted that Clause 23.1 prohibited the advertising of prescription only medicines to the public. Clause 23.2 permitted information to be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine.

The Panel noted that when entering the www.monofer.com site, a pop-up window appeared which stated 'Welcome to Pharmacosmos' international Monofer website. This medical website focuses om [sic] Monofer (iron isomaltoside 1000), a treatment for iron deficiency anemia'. The health professional site was visible behind the pop-up window. The Panel noted from the screenshot that the phrases: 'High dose Infusi', 'up to 20', and 'High dose iron' were entirely visible and part of the letters that formed the words 'in just one visit' were visible

on a photograph showing a hand holding a vial of Monofer. The Panel considered that even though only part of the letters that formed the words 'in just one visit' were visible, the claim 'High dose iron in just one visit' was readable. The next question for the Panel to consider was whether the visible claims were promotional for Monofer or whether the page at issue was in line with the requirements of Clause 23.2.

The Panel noted Pharmacosmos' submission that readers accessed the site because they were already seeking information about Monofer. The Panel noted that members of the public would be able to access the Monofer SPC on the eMC which would include the product's indication. The supplementary information to Clause 23.2 made it clear that a number of materials including the SPC could be made available as a resource for the public/patients. The Panel considered that the pop-up window in combination with promotional claims for Monofer intended for health professionals which were visible to members of the public meant that a prescription only medicine had been promoted to the public who would also be encouraged to ask their health professionals to prescribe it. Breaches of Clauses 23.1 and 23.2 were ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The complainant alleged that the Monofer SPC on the website was out of date. The Panel noted Pharmacosmos' submission that after a review of all IV iron products in Europe by the EMA in September 2013, an update of the SPCs for all of these products was recommended. The Panel noted Pharmacosmos' submission that the update of the Monofer SPC was currently under review by the regulatory authorities and, as yet, no formal changes had been approved. Pharmacosmos also submitted that the SPC on Monofer.com was the correct and current version. The Panel did not consider that the complainant had established that the Monofer SPC on the website was out of date. Thus the Panel ruled no breach of Clause 7.2 and consequently ruled no breach of Clauses 9.1 and 2.

The Panel noted that Clause 7.11 stated that the word 'new' must not be used to describe any product or presentation which has been generally available, or any therapeutic indication which has been generally promoted, for more than twelve months in the UK. The Panel noted Pharmacosmos' submission that that the word 'new' should no longer have appeared when referring to Monofer's iron matrix technology. Monofer had been available for several years. A breach of Clause 7.11 was ruled as acknowledged by the company. The website had been updated in this regard.

COMMENTS FROM PHARMACOSMOS

At the same time as it was advised of the complaint, Pharmacosmos UK was invited to join the PMCPA list of non-member companies which had agreed to comply with the Code. In response, and before it was advised of the Panel's rulings above, Pharmacosmos submitted that it had given this invitation serious consideration and it was fully committed to ethical promotion of its products; however, it found the current approach to dealing with complaints within the PMCPA Constitution and Procedure increasingly challenging to manage. As a result, it declined the offer to join the PMCPA list of non-member companies.

Pharmacosmos submitted that there were a number of reasons for this decision and it highlighted a couple. Pharmacosmos found anonymous complaints highly problematic, it had over the last year or so, received a number of anonymous complaints. These complaints had clearly been submitted by individuals with an intimate knowledge of the Code and the IV iron market. One of Pharmacosmos' competitors, Takeda, had also received an anonymous complaint recently.

Pharmacosmos submitted that processing such cases to provide an adequate response for the PMCPA was very time consuming. By submitting the complaint anonymously the complainant bypassed inter-company dialogue and had no risk of penal fees for unsubstantiated complaints, mechanisms that would normally serve to keep the number of PMCPA cases to a relevant minimum.

In addition, Pharmacosmos found it highly problematic that the PMCPA made rulings concerning products without consulting the relevant marketing authorisation holders to ensure the correctness of the information provided by the different parties.

Pharmacosmos submitted that the recently published case, Case AUTH/2623/7/13 Anonymous v Takeda, contained several incorrect statements on its product Monofer made by the anonymous complainant, Takeda, and the Panel.

Pharmacosmos considered this was another example of how a complainant was abusing the Panel and the Code to influence market perception incorrectly – this time with regard to stipulating incorrect dosing limitations on the use of Monofer in haemodialysis patients (albeit not in a complaint about Pharmacosmos itself).

Given these numerous examples of misuse of the self-regulatory system and after careful consideration, Pharmacosmos had decided not to join the list of non-member companies neither as Pharmacosmos A/S or Pharmacosmos UK. Pharmacosmos stated that it had been involved in a number of inter-company complaints via the PMCPA over the last four years. The clear majority of rulings had been in favour of Pharmacosmos which showed its commitment to ethical promotion of its products in the past. Although Pharmacosmos' association with the PMCPA was now ended, it welcomed the constructive nature of its historical interactions. Pharmacosmos stated that it would continue to be fully committed to the ethical promotion of its products moving forward.

Pharmacosmos advised that it had already changed the material at issue. It referred to the letter it had sent to the PMCPA before it received the Panel's decision.

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The Authority noted that Pharmacosmos no longer wished to accept the jurisdiction of the Authority and did not complete and return the form of undertaking and assurance. The Authority was bound by Paragraph 11.4 of the Constitution and Procedure to report the company to the Code of Practice Appeal Board.

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COMMENTS FROM PHARMACOSMOS ON THE REPORT

Pharmacosmos did not attend the Appeal Board meeting for the consideration of the report and had no further comments on the case.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE AUTHORITY

The Appeal Board noted that Pharmacosmos A/S had previously agreed to abide by the Code as a non member company. The complaint in this case was the first one which involved Pharmacosmos UK so that company had been invited to join the list of non member companies that agreed to comply with the Code and accept the jurisdiction of the PMCPA.

The Appeal Board noted the reasons given by Pharmacosmos for its decision not to join the list of non member companies that had agreed to comply with the Code and accept the jurisdiction of the PMCPA, in particular its views about anonymous complaints. The Appeal Board noted that the PMCPA had always dealt with anonymous complaints, regardless of whether the complainant was contactable or not, and although it was preferable that complainants were not anonymous consideration of such complaints by the PMCPA was an important element of robust self regulation.

The Appeal Board noted Pharmacosmos' submission that it had changed the material at issue. However, the Appeal Board noted that by failing to provide the requisite undertaking and assurance Pharmacosmos had failed to comply with the procedure set out in Paragraph 7 of the Constitution and Procedure and thus the Appeal Board decided, in accordance with Paragraph 11.4 of the Constitution and Procedure, to remove Pharmacosmos from the list of non member companies which had agreed to comply with the Code*. Responsibility for Pharmacosmos under the Code could no longer be accepted. The Medicines and Healthcare Products Regulatory Agency (MHRA) and the ABPI Board of Management were subsequently advised of the Appeal Board's decision.

Pharmacosmos UK submitted that it could not be removed from the non-members list as it had never formally agreed to join it. Pharmacosmos A/S and Pharmacosmos UK had, however, between 2010 and April 2014, each demonstrated their willingness to voluntarily comply with the Code and accept the jurisdiction of the Authority both in terms of complaints received and complaints submitted and in that regard both appeared to consider themselves effectively, if not formally, on the non members list.

Complaint received	**16 January 2014**
Report to Appeal Board	**24 July 2014**
MHRA informed	**24 June 2014 and 4 August 2014**
ABPI Board informed	**4 August 2014**

CASE AUTH/2705/3/14

ROCHE v MERCK SERONO

Presentation of Erbitux clinical trials results in a press release

Roche complained about the way in which Merck Serono represented the results of the FIRE-3 AIO (Arbeitgemeinschaft Internistische Onkologie) clinical trial in a UK press release issued 28 September 2013 and also raised concerns about such data in unidentified Erbitux (cetuximab) promotional materials.

At that time Erbitux was indicated, *inter alia*, for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer (mCRC) in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX (folinic acid, fluorouracil and oxiplatin), and as a single agent in patients who had failed oxaliplatin and irinotecan-based therapy and who were intolerant to irinotecan.

Roche marketed Avastin (bevacizumab) which was indicated, *inter alia*, in combination with fluoropyrimidine-based chemotherapy for the treatment of adult patients with metastatic carcinoma of the colon or rectum.

The detailed response from Merck Serono is given below.

Roche explained that the FIRE-3 study trial evaluated the superiority of cetuximab plus combination chemotherapy, compared with bevacizumab plus combination chemotherapy in the first-line treatment of KRAS wild-type mCRC. The primary endpoint for the study was overall response rate. Secondary endpoints included progression-free survival and overall survival. Importantly it was not a treatment sequencing study as subsequent lines of treatment were not specified.

Roche stated that the primary analysis of the study, presented at the American Society of Clinical Oncology (ASCO) 2013, showed that the study failed to reach its primary endpoint. There was no significant difference in overall response rate (primary endpoint) between the two treatment arms. There was also no significant difference in progression-free survival between the two arms, but increased overall survival in the arm receiving cetuximab plus chemotherapy as first-line treatment (one of the secondary endpoints) was reported. The Kaplan-Meier curves of overall survival presented at ASCO 2013 showed that the lines, representing the different study arms, did not begin to separate until the 15-18 month time point. Given that the median time to first progression was approximately 10 months in both arms and the reported median duration of first-line treatment was significantly shorter than this in both arms, there would appear to be significant grounds to question the degree to which the first-line treatment was responsible for any overall survival difference demonstrated.

Roche noted that a second FIRE-3 analysis presented in July 2013 at the World Congress on Gastrointestinal Cancer, provided details of the second-line treatments administered to patients in the FIRE-3 trial. This analysis showed differences in the treatments received in the second-line setting by patients in the two arms. A further FIRE-3 analysis presented at the European Society for Medical Oncology (ESMO) European Cancer Congress (ECC), October 2013, showed the results of a pre-planned exploratory analysis of a sub-group of patients who were not only KRAS wild-type, but also NRAS wild-type (termed RAS wild-type). In that new sub-group of patients, the first-line cetuximab plus chemotherapy arm again failed to show a significant improvement over the bevacizumab plus chemotherapy arm in both overall response rate and progression free survival. However, the analysis showed a difference of 7.5 months in median overall survival between the two arms in favour of the group receiving cetuximab plus chemotherapy as their first-line regimen. As for the previous KRAS overall survival analysis, the Kaplan-Meier curves did not separate until well after completion of first-line treatments and first progression.

Merck Serono's press release about the FIRE-3 trial analysis after the ESMO-ECC congress was headed: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'. Roche stated that the press release was the source material for at least one article in the medical press and similar messages were used in promotional materials in Ireland (with prescribing information stating it was for UK and Ireland) but was not sure if it was being used in the UK.

Roche alleged that the overall survival statement in the heading 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study' was misleading because the FIRE-3 study failed to reach its primary endpoint of overall response rate. The heading was based on a sub-group analysis from this 'negative' phase III study. The fact that the study did not meet its primary endpoint was not prominently presented in the press release; it was only mentioned midway down the second page. Roche alleged a breach. Findings from secondary endpoints must be set within the context of the primary endpoints companies could not 'cherry pick' favourable findings.

The Panel noted that the press release was dated 28 September 2013 and thus the relevant Code was the Second 2012 Edition (amended) Code.

The Panel noted that the press release was headed 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study', below the heading in slightly smaller text were two bullet points; 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 to 33.1 months (p=0.011) in mCRC patients with RAS wild-type tumours receiving 1st line Erbitux plus FOLFIRI compared with patients receiving bevacizumab plus FOLFIRI' and 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'.

Text beneath referred to the phase III head-to-head trial which showed a 'clinically relevant improvement from Erbitux (cetuximab) plus FOLFIRI vs bevacizumab plus FOLFIRI as first-line treatment in metastatic colorectal cancer (mCRC) in patients with RAS wild-type tumours'.

The Panel noted that the FIRE-3 study was a multicentre randomised phase III trial investigating 5-FU, folinic acid and irinotecan (FOLFIRI) plus cetuximab vs FOLFIRI plus bevacizumab in first-line treatment of mCRC. The study failed to meet its primary endpoint of overall response rate (ORR). Secondary endpoints included median progression free survival (PFS) and median overall survival.

The summary of the FIRE-3 study principal investigator's presentation at the European Cancer Congress stated 'OS was markedly superior (Δ = 7.5 months, HR 0.70) in all RAS wild-type patients receiving first-line therapy with cetuximab (p=0.011)'. The presentation concluded that upfront determination of RAS (KRAS and NRAS) mutation status appeared to be highly recommendable in patients with metastatic disease and concluded that 'Patients with all-RAS wild-type tumours have a clinically relevant survival benefit when first-line treatment with cetuximab is offered'.

The Panel disagreed with Merck Serono's decision that as the lack of difference in ORR and PFS had previously been reported in the ASCO press release and as there was no change in these endpoints it was not considered appropriate to include them in the heading. The Panel considered that the heading, 'Merck Serono's Erbitux Significantly Extends Survival to 7.5 Months in mCRC Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study', was not a fair reflection of the overall data; it had not been placed within context of the study's primary outcome. The reference to the study's failure to meet its primary endpoint of objective response rate based on investigators' read in patients with KRAS EXON 2 wild-type tumours appeared in the third paragraph on page 2 and was insufficient to counter the heading. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the secondary endpoint findings. The heading was therefore misleading as alleged and the Panel ruled a breach of the Code. This ruling was upheld on appeal by Merck Serono.

Roche stated that the first bullet point: 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 months to 33.1 months (p=0.011) …' was the result of a sub-group analysis from the negative phase III study. Further contextualisation outlined in the background section was critical for the audience to be able to understand the clinical relevance. The press release failed to set the finding clearly in the context of the overall study which failed to meet its primary endpoint. In addition, the word 'exploratory' was only used much later in the press release to describe that analysis. Roche alleged that this rendered the press release misleading.

Roche was concerned about the statistical validity of the analysis, as any sub-group analyses needed to be accounted for statistically to avoid bias from multiple analyses. It was acknowledgement later in the press release that the analysis was exploratory, this should have been reflected in the headlines/bullet points to avoid misleading the audience. In inter-company dialogue, Merck Serono was unable to comment on Roche's statistical concerns and directed Roche to the study sponsor. This had not reassured Roche that Merck Serono could sufficiently substantiate the data and Roche alleged a breach of the Code.

The Panel considered that its general comments above in relation to the heading of the press release were relevant here. The sub-group analyses had not been placed in context of the study's failure to achieve its primary endpoint. In addition, it was not clear at the outset that the data was from a pre-planned exploratory analysis. The only reference to this was on the second page and there was no explanation that no confirmatory clinical conclusions could be drawn from such an analysis. In the Panel's view the press release invited the reader to draw such conclusions. Exploratory analyses should not be used as the basis for a robust comparison of medicines. The material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The Panel considered that the bullet point was misleading as alleged and ruled a breach of the Code. This ruling was upheld on appeal by Merck Serono.

The Panel noted Roche's allegation that Merck Serono was unable to substantiate the sub-group analysis. Merck Serono submitted that the bullet point in question was supported by the data presented at ESMO. However, the Panel noted that the ESMO presentation did not appear to cover statistical analysis of the sub-group although the abstract made it clear that the analysis was pre-planned. The Panel however did not have any accompanying transcript.

The Panel noted Roche's allegation that the sub-group analysis needed to be accounted for statistically to avoid bias from multiple analyses. On balance and on this very narrow point the Panel ruled that the bullet point in question was not capable of substantiation. A breach of the Code was ruled. This ruling was appealed by Merck Serono.

The Appeal Board noted that this was clearly a complex area. As the FIRE-3 study had progressed

it had started to become clear that patients with RAS wild-type mCRC responded better to therapy than those with RAS mutations. The analysis at issue in the press release involved only the RAS wild-type patients (n=342) and not the original ITT population (n=592). Although the Erbitux marketing authorisation had been restricted to patients with RAS wild-type mCRC, this was not the case when the press release was issued on 28 September 2013. In that regard the Appeal Board considered that only the data that was available on that date could be relied upon to substantiate the content of the press release.

The Appeal Board although concerned as to whether the analysis was sufficiently powered, considered that the bullet point was nonetheless factually correct and thus on balance, on this very narrow point, was capable of substantiation. No breach of the Code was ruled. The appeal on this point was successful.

Roche alleged that the second bullet point: 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)' seemed to suggest that there was no difference between the arms with respect to overall survival in the sub-group of patients with RAS mutant mCRC. In Europe, cetuximab was not licensed in RAS mutant mCRC and was actually contraindicated in the treatment of RAS mutant mCRC with certain chemotherapy combinations. No such restriction applied to bevacizumab. The licence restriction, or indeed any of the licence particulars (eg should only be used for EGFR-expressing tumours) for cetuximab were not mentioned in the press release.

The comparison was actually based on a pooled analysis of two different populations of patients with RAS mutations. There was no information in the press release that these findings were based on pooling data from two different time points, using two different testing methods. In 2008, patients with mutations in the KRAS EXON 2 gene were no longer included in the licences for anti-EGFRs in Europe. As a result of this, the FIRE-3 trial was amended in 2008 to exclude recruitment of patients with KRAS MT gene in EXON 2. The analysis based on patients with RAS MT mCRC recruited into the trial after the protocol amendment reported a median overall survival of 16.4 months in the cetuximab arm and 20.6 months in the bevacizumab arm. With the press release only utilising the pooled analysis data set it appeared that there was no difference in overall survival between the treatment arms without clarification that cetuximab was unlicensed (or even contraindicated) in patients with RAS MT disease.

Roche was extremely concerned that the claim implied cetuximab had efficacy in a population for which it was unlicensed or contraindicated as it compared itself with a medicine that was licensed for use in that population. The statement, whilst factually accurate, did not provide balance, was misleading in itself and with respect to the safety profile of cetuximab and did not encourage rationale use of the medicine.

The Panel considered that the comparison was misleading as it was not clear that it was based on a pooled analysis of two different populations of patients with RAS mutations from two different time points. The Panel ruled breaches of the Code as it considered that the context of the comparison was not clear and it was therefore misleading.

The Panel disagreed with Merck Serono's submission that the comparison made no efficacy claims for cetuximab. The Panel considered that the overall survival comparison of cetuximab with bevacizumab in patients with any RAS mutations was misleading as it implied that like bevacizumab, cetuximab was licensed for the treatment of RAS mutant mCRC which was not so. It was only licensed for EGFR expressing RAS wild-type metastatic colorectal cancer. In the Panel's view the failure of Merck Serono to place the bullet point within the context of cetuximab's licensed indication and the failure to mention relevant contraindications was misleading and did not encourage the rational use of cetuximab and breaches of the Code were ruled. A breach was also ruled as the comparison was misleading.

The Panel noted Merck Serono's submission that the press release had been widely distributed to medical journals and health journalists. The Panel noted its rulings above in relation to the misleading statements made about Erbitux and considered that in relation to the matters discussed above the press release, which had been made available to the public, was not factual and had not presented information about Erbitux, a prescription only medicine, in a balanced way and a breach was ruled.

Roche alleged that the quotation on page 2: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies…' was misleading as it did not contextualise the sub-group analysis. In addition, whilst it reflected the views of the investigator, the discussant at ESMO strongly questioned it and recommended that based on the available data it was not a paradigm shift and the forthcoming results of CALGB (a forthcoming study evaluating the efficacy of first-line cetuximab vs first-line bevacizumab with a primary endpoint of overall survival) should be awaited to provide more insights into the outcomes of FIRE-3. Using words as strong as 'paradigm shift' in a press release was exaggerated and could raise unfounded hopes and Roche alleged breaches of the Code.

Overall, given the number and nature of its concerns and the very real risk to patient safety, Roche alleged that the press release and promotional materials failed to maintain high standards. Roche also alleged that such a concerted campaign based on misleading and unbalanced claims of this nature put patient safety at risk and brought the industry into disrepute in breach of Clause 2.

The Panel noted its comments and rulings at above with regard to the data from the FIRE-3 study showing a 7.5 month increase in median overall survival when using Erbitux plus FOLFIRI as compared with using bevacizumab plus FOLFIRI in metastatic colorectal cancer. The Panel considered that the quotation 'Such a prolongation

is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies' was misleading as within the context of the median survival data it applied disproportionate weight to the results thereby exaggerating Erbitux's properties and consequently it did not encourage rational use. The Panel thus ruled breaches of the Code. The Panel noted its comments above regarding the provision of information to the public and similarly ruled a further breach of the Code. These rulings were upheld on appeal by Merck Serono.

The Panel considered that Merck Serono had failed to maintain high standards and ruled a breach in that regard.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel noted that Roche had referred to patient safety. The Panel noted its rulings of breaches of the Code above. The Panel considered that it was very important that press releases about sensitive issues such as survival in cancer were fair, factual and not misleading. The press release had failed to reflect the study's primary endpoint and the product's licensed indications. In particular the headline claim about survival had been ruled in breach of the Code. The Panel considered that on balance the circumstances warranted such a ruling and a breach of the Clause 2 was ruled. This ruling was upheld on appeal by Merck Serono.

Roche Products Ltd complained about Merck Serono Limited's presentation showing the results of the FIRE-3 AIO (Arbeitgemeinschaft Internistische Onkologie) clinical trial in a UK press release (ref ERB13-0152) issued 28 September 2013 and also raised concerns about such data in unidentified Erbitux (cetuximab) promotional materials.

At that time Erbitux was indicated, *inter alia*, for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer (mCRC) in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX (folinic acid, fluorouracil and oxiplatin), and as a single agent in patients who had failed oxaliplatin and irinotecan-based therapy and who were intolerant to irinotecan.

Roche marketed Avastin (bevacizumab) which was indicated, *inter alia*, in combination with fluoropyrimidine-based chemotherapy for the treatment of adult patients with metastatic carcinoma of the colon or rectum.

In its response, Merck Serono stated that the press release was issued in the UK on 30 September 2013 and was sent to 40 medical and pharmaceutical titles, 23 health journalists at national print and online titles and 16 freelance health journalists.

COMPLAINT

Roche alleged that Merck Serono was in breach of Clauses 2, 7.2, 7.3, 7.4, 7.10, 9.1, 10.2, 12 and 22.2. Roche explained that the FIRE-3 clinical trial evaluated the superiority of cetuximab plus combination chemotherapy, compared with bevacizumab plus combination chemotherapy in the first-line treatment of KRAS wild-type metastatic colorectal cancer. The primary endpoint for the study was overall response rate. Secondary endpoints included progression-free survival and overall survival. Importantly it was not a treatment sequencing study as subsequent lines of treatment were not specified within the study protocol.

Roche stated that the primary analysis of the FIRE-3 study was presented at the American Society of Clinical Oncology (ASCO) 2013 and showed that the study failed to reach its primary endpoint. There was no significant difference in overall response rate (primary endpoint) between the two treatment arms. There was also no significant difference in progression-free survival between the two arms, but the authors reported increased overall survival in the arm receiving cetuximab plus chemotherapy as their first-line treatment (one of the secondary endpoints). The Kaplan-Meier curves of overall survival presented at ASCO 2013 showed that the lines, representing the different study arms, did not begin to separate until the 15-18 month time point. Given that the median time to first progression was approximately 10 months in both arms (10.0 and 10.3 months) and the reported median duration of first-line treatment was significantly shorter than this in both arms, there would appear to be significant grounds to question the degree to which the first-line treatment was responsible for any overall survival difference demonstrated.

Roche further stated that a second FIRE-3 analysis was presented in July 2013 at the World Congress on Gastrointestinal Cancer providing details of the second-line treatments administered to patients in the FIRE-3 trial. This analysis showed differences in the treatments received in the second-line setting by patients in the two arms. Furthermore, a large proportion of patients in FIRE-3 received treatment combinations in the second-line setting which were not current standard practice and were unavailable in the UK (as defined by the Cancer Drugs Fund listings) and were not prescribed newer options now available after first-line bevacizumab (eg aflibercept) – making FIRE-3 of questionable relevance to current UK clinical practice.

Roche stated that a further FIRE-3 analysis presented at the European Society for Medical Oncology (ESMO) European Cancer Congress (ECC), October 2013, showed the results of a pre-planned exploratory analysis of a sub-group of patients who were not only KRAS wild-type, but also NRAS wild-type (termed RAS wild-type). In that new sub-group of patients, the first-line cetuximab plus chemotherapy arm again failed to show a significant improvement over the bevacizumab plus chemotherapy arm in both overall response rate and progression free survival. However, the analysis showed a difference of 7.5 months in median overall survival between the two arms in favour of the group receiving cetuximab plus chemotherapy as their first-line regimen. As for the previous KRAS overall survival analysis, the Kaplan-Meier curves did not separate until well after completion of first-line treatments and first progression.

Roche became aware of a UK Merck Serono press release relating to the FIRE-3 trial analysis following the ESMO–ECC congress. The press release was headed: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'. Roche alleged that this press release was the source material for at least one media article 'Oncology Times', a journal with a readership of approximately 7,000 cancer professionals not restricted to oncologists. At the same time Roche was aware of similar messages being used in promotional materials in Ireland (with prescribing information stating it was for UK and Ireland) but was not sure if it was being used in the UK. Roche asked Merck Serono during inter-company dialogue on 4 December 2013 whether the statements were being used in promotional materials. Merck Serono did not confirm on this point until 3 February 2014.

Roche's specific concerns about the press release were as follows:

1 **Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study'**

Roche alleged that the overall survival statement in this heading was misleading because the FIRE-3 study failed to reach its primary endpoint of overall response rate. The heading was based on a sub-group analysis from this 'negative' phase III study. The fact that the study did not meet its primary endpoint was not prominently presented in the press release but was only mentioned midway down the second page of the press release. Roche alleged a breach of Clause 7.2 as the full nature of the study results were not represented in the heading or summary bullet points. There was well-established case precedent and Medicines and Healthcare Products Regulatory Agency (MHRA) Guidance that findings from secondary endpoints must be set within the context of the primary endpoint and that companies could not 'cherry pick' favourable findings. Merck Serono had now confirmed that it was using similar claims in its promotional materials. Given Merck Serono's uncompromising position that prominent qualification of such claims was not necessary, Roche strongly suspected that promotional materials currently in use would also not have the overall survival findings set in the context of the primary endpoint.

2 **First bullet point: 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 months to 33.1 months (p=0.011) …'**

Roche stated that this was the result of a sub-group analysis from the negative phase III study. Further contextualisation outlined in the background section was critical for the audience to be able to understand the clinical relevance of the data. The press release failed to set the finding clearly in the context of the overall study which failed to meet its primary endpoint. That key point was only briefly mentioned in paragraph 3, on the second page. In addition, the word 'exploratory' was only used much later in the press release to describe that analysis. Roche alleged that this rendered the press release misleading in breach of Clause 7.2.

Roche had stressed to Merck Serono that its concern with the analysis was not related to the number of patients included in the study but to the statistical validity of the analysis, as any sub-group analyses needed to be accounted for statistically to avoid bias from multiple analyses. It was acknowledged later in the press release that the analysis was exploratory therefore Roche would have anticipated that being reflected in the headlines/bullet points of the press release to avoid misleading the audience. Through inter-company dialogue, Merck Serono had submitted that it was unable to comment on Roche's statistical concerns and directed Roche to the study sponsor. This had not reassured Roche that Merck Serono was able to sufficiently substantiate the data it had used in its press release as it should have full awareness of the validity and relevance of data it used in a press release and promotional material. On the basis of that statement, received in the last round of inter-company dialogue, Roche alleged a breach of Clause 7.4.

Merck Serono eventually admitted, as Roche suspected, that similar claims were also being used in promotional materials and again, given its uncompromising stance in defence of the unqualified claim, Roche was extremely concerned at similar breaches in Merck Serono's promotional materials.

3 **Second bullet point: 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'**

Roche alleged that this bullet point seemed to serve no other purpose than to suggest that there was no difference between the arms with respect to overall survival in the sub-group of patients with RAS mutant mCRC. In Europe, cetuximab was not licensed in RAS mutant mCRC and was actually contraindicated in the treatment of RAS mutant mCRC with certain chemotherapy combinations. No such restriction applied to bevacizumab. The licence restriction, or indeed any of the licence particulars (eg should only be used for EGFR-expressing tumours) for cetuximab were not mentioned in the press release.

The comparison was actually based on a pooled analysis of two different populations of patients with RAS mutations (KRAS mutation pool EXON 2 according to Annals of Oncology, 2012, dated from 2006 to 2008 and advanced RAS mutation analysis of the FIRE-3 trial with mutations in EXON 3 and 4 of KRAS and EXON 2, 3, and 4 of the NRAS gene, which were included from October 2008). There was no information in the press release that these findings were based on pooling data from two different time points, using two different testing methods. In 2008, patients with mutations in the KRAS EXON 2 gene were no longer included in the

licences for anti-EGFRs in Europe. As a result of this, the FIRE-3 trial was amended in 2008 to exclude recruitment of patients with KRAS MT gene in EXON 2. The analysis based on patients with RAS MT mCRC recruited into the trial after the protocol amendment reported a median overall survival of 16.4 months in the cetuximab arm and 20.6 months in the bevacizumab arm. With the press release only utilising the pooled analysis data set it appeared that there was no difference in overall survival between the treatment arms without clarification that cetuximab was unlicensed (or even contraindicated) in patients with RAS MT disease. Although that may not be considered a breach of Clause 3.2 as a press release should be non-promotional it was certainly not in the spirit of the Code to make claims for a population outside the licence or contraindicated.

Roche was extremely concerned that the claim implied cetuximab had efficacy in a population for which it was unlicensed or contraindicated as it compared itself with a medicine that was licensed for use in that population. Merck Serono through inter-company dialogue did not share Roche's concerns with the statement and had indicated that it was included in the press release for balance. The statement, whilst factually accurate, did not provide balance and was misleading in itself and with respect to the safety profile of cetuximab. As such, it did not encourage rationale use of the medicine. Roche alleged a breach of Clauses 7.2, 7.3, and 7.10 and 22.2.

Whilst Merck Serono's latest letter dated 3 February 2014, assured Roche that that claim was not being used in promotional materials, Roche remained extremely concerned that Merck Serono failed to acknowledge the inappropriateness of including this bullet point in a press release, and the potentially serious consequences for patient safety.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies…'

Roche alleged that the quotation was misleading as it did not contextualise the sub-group analysis. In addition, whilst it reflected the views of the investigator, the discussant at ESMO strongly questioned it and recommended that based on the available data it was not a paradigm shift and the forthcoming results of the CALGB study (a forthcoming study evaluating the efficacy of first-line cetuximab vs first-line bevacizumab with a primary endpoint of overall survival) should be awaited to provide more insights into the outcomes of FIRE-3. Based on the nature of the analysis, a statement made in that way and using words as strong as 'paradigm shift' in a press release was exaggerated and could raise unfounded hopes. Roche alleged a breach of Clauses 7.2, 7.10, 10.2 and 22.2.

Based on its concerns, during inter-company dialogue, Roche requested that Merck Serono publish an erratum notice in relation to the article that appeared in the Oncology Times. Merck Serono declined this request as the companies had not resolved their concerns through inter-company dialogue. However, Roche was disappointed that Merck Serono did not consider it was responsible for press coverage that had been reproduced faithfully from its press release.

5 Overall

Given the number and nature of its concerns and the very real risk to patient safety, combined with Merck Serono's blunt refusal to relent on any of the points raised through inter-company dialogue, Roche alleged that the press release and promotional materials were in breach of Clause 9.1 as high standards had clearly not been maintained in the development of the items. Roche also alleged that such a concerted campaign based on misleading and unbalanced claims of this nature put patient safety at risk and in doing so, brought the industry into disrepute and was a breach of Clause 2.

RESPONSE

To give background and context to the complaint, Merck Serono submitted that the FIRE-3 study was conducted by the collaborative German AIO study group and was the first head to head comparison of cetuximab and bevacizumab in conjunction with a FOLFIRI chemotherapy backbone in the first-line treatment of KRAS wild-type (KRAS-wild-type) metastatic colorectal cancer. The primary endpoint was overall response rate (ORR) and the secondary endpoints included progression-free survival (PFS) and overall survival (OS). In addition to randomisation between the two arms the protocol included a recommendation with respect to second-line therapy. The appropriate page from the protocol was provided.

Merck Serono stated that FIRE-3 was initially presented at ASCO 2013 by the FIRE-3 study principal investigator and a copy of the abstract for the study was provided, the conclusion of which was that:

> 'ORR was comparable between arms in the ITT analysis, but favoured Arm A in assessable patients. Significantly superior OS was observed in KRAS-WT patients receiving cetuximab plus FOLFIRI as first-line treatment.'

The FIRE-3 principal investigator also stated in his presentation that:

> 'First-line treatment with FOLFIRI [folinic acid, fluorouracil and irinotecan] plus cetuximab resulted in a clinically meaningful difference in median OS of 3.7 months (HR 0.77) when compared to FOLFIRI plus bevacizumab.'

Merck Serono submitted that FIRE-3 was also considered of sufficient importance to be included in a press release by ASCO and a copy of the relevant sections was provided with independent comment on the study.

Merck Serono submitted that a further analysis of FIRE-3 was presented at the World Congress on Gastrointestinal Cancer (WGIC). Roche stated that 'there were differences in the treatments received in the second-line setting by patients in the two arms',

however data presented at the meeting showed that the chemotherapy backbone was very well balanced and similar numbers continued on the initial treatment strategy or switched to the alternate investigational agent. One of the conclusions was that:

> 'Frequencies of **antibody cross-over and continuation beyond progression** as well as chemotherapies were **balanced** in 2nd line treatment based on current evidence.'

Merck Serono noted that Roche had suggested that FIRE-3 was of 'questionable relevance to current UK practice'. However the use of cetuximab plus FOLFIRI followed by bevacizumab plus FOLFOX for the treatment of RAS wild-type metastatic colorectal cancer was subsequently endorsed by and added to the National Cancer Drugs Fund list and hence FIRE-3 was highly relevant to UK clinicians. Further evidence of the relevance to UK clinicians was the recently updated East Midlands Cancer Network guidelines for the treatment of metastatic colorectal cancer which included the cetuximab and FOLFIRI regimen used in FIRE-3 as a first-line treatment.

Merck Serono submitted that a pre-planned analysis of FIRE-3 investigating the effect of further mutations was presented at the ESMO-ECC congress. Merck Serono provided the presentation which showed that those patients who were both KRAS and NRAS wild-type - RAS wild-type - showed a difference of 7.5 months in OS in favour of the cetuximab arm over the bevacizumab arm.

An ESMO spokesperson commented on the study:

> 'The results show that the better RAS mutations can improve both the ORR and the OS in patients receiving cetuximab as compared to bevacizumab. This highlights the importance for detecting other RAS mutations to better select the group of patients who might benefit from anti-EGFR moAbs. These results might have an impact on daily clinical decisions as we are able to define a sub-group of patients most likely to benefit from FOLFIRI plus cetuximab in first-line setting.'

Similar prolongations in survival in the RAS wild-type population had been seen with another anti-EGFR agent, panitumumab, resulting in a change in the marketing authorisations of both agents to use in RAS wild-type patients only.

Merck Serono submitted than in summary, FIRE-3 had been shown to be of significant interest to ASCO, ESMO and the wider clinician community. The clinically significant increase in overall survival, particularly in the RAS wild-type group, led to debate regarding treatment strategy and the optimal use of biological agents in combination with chemotherapy. FIRE-3 was an ongoing study and questions around lack of difference in progression free survival remained to be answered. However, for Roche to describe FIRE-3 as a 'negative' study showed a wilful disregard for its important results.

Merck Serono's responded to Roche's specific concerns the press release as follows:

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study'

Merck Serono submitted that the heading was a factual description of the results of the new RAS wild-type analysis as presented at ESMO and was the only parameter that had significantly changed from the presentations at ASCO or WGIC. Furthermore the improvements in overall survival had been highlighted in the abstracts from both ASCO and ESMO so for Roche to allege that Merck Serono was 'cherry picking' data was a misrepresentation of the study results as presented by the investigators.

Merck Serono had always acknowledged that the primary endpoint of the study was not met and that was contained in the third paragraph of the press release immediately after the new results. The lack of difference in ORR and PFS had been reported in the ASCO press release and as there was no change in those endpoints it was not felt appropriate to include them in the headline.

Merck Serono confirmed that a similar claim regarding overall survival was being used in promotional material. That claim was always set in context and the wording 'The primary endpoint of ORR was not met in this study' was displayed on all materials where the claim was made.

Merck Serono submitted that the press release was factually correct, reflected the important results from a new analysis and acknowledged that the primary endpoint was not met. Accordingly the information was accurate, fair and reflected the evidence and was therefore not in breach of Clause 7.2.

2 First bullet point: 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 months to 33.1 months (p=0.011) …'

Merck Serono submitted that this was a large sub-group with 407 (69%) patients, the majority of the study population, evaluable for RAS status. The numbers evaluable for RAS status were balanced in both arms of the study and the statement was based on data presented at ESMO.

The summary of the presentation also included the statement:

> 'The RAS evaluable population was in all respects comparable to the ITT population.'

And concluded:

> 'Patients with all-RAS wild-type tumours have a clinically relevant survival benefit when first-line treatment with cetuximab is offered.'

Merck Serono submitted that the word 'exploratory' reflected that this was the first major study to evaluate RAS testing with Erbitux and reflected recent evidence that led the CHMP to recommend a change to the marketing authorisation for Erbitux from KRAS wild-type patients to all RAS wild-type metastatic colorectal cancer.

With regard to Roche's concerns regarding the statistical validity of the analysis, Merck Serono stated that these concerns had only been raised by Roche and had not been raised by either discussants at ASCO, WCGIC and ESMO or by any clinician to Merck Serono in the UK or elsewhere. Merck Serono disagreed that Roche's concerns that '…407 represents a large percentage of patients from the original ITT population but any sub-group analyses needs to be adjusted for statistically to avoid the issue of multiplicity arising from multiple analyses. Sub-groups may also be confounded as the benefits of the original randomisation are lost even if there are equal numbers of patients in the two groups' were valid in this case. The AIO study group which conducted the study, was a large and well respected group and was, in Merck Serono's view, competent to conduct an analysis of the data. Accordingly, Roche was advised that its concerns should be addressed to the AIO investigators directly who would be best placed to assist.

Merck Serono submitted that the bullet point again reflected the data as presented at ESMO, the importance of which was acknowledged by the ESMO spokesperson, and did not breach Clause 7.2. All claims were referenced to recently presented data, were capable of independent substantiation, and did not breach Clause 7.4.

3 Second bullet point: 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'

Merck Serono pointed out that information on the efficacy of Erbitux in both the KRAS wild-type and mutant populations and RAS wild-type and mutant populations were in Section 5.1 of the summary of product characteristics (SPC). This bullet point was included to provide full disclosure and reflected the data as presented at ESMO.

Merck Serono submitted that it took great care to ensure appropriate use of cetuximab though a variety of materials and services. Merck Serono had provided free KRAS testing to the NHS since the marketing authorisation was changed initially and now provided additional NRAS testing to ensure that clinicians could make a decision regarding what they considered to be appropriate for each patient by knowing the tumour biology, through the RAS biomarkers. Only with this knowledge could some treatments be included in or excluded from a patient's treatment plan. The availability of appropriate biomarker testing was deemed so essential to the appropriate use of anti-EGFR therapies such as cetuximab and panitumumab that the service would be taken over by NHS England from May 2014.

This press release was the only mention by Merck Serono of these data. Merck Serono was well aware that the marketing authorisation for cetuximab limited the use of cetuximab to only RAS wild-type patients and all promotional materials made this absolutely clear. [At the time of the press release Erbitux was indicated for KRAS wild-type patients]. Merck Serono submitted that Roche had wilfully misinterpreted this bullet point to manufacture a safety concern. Indeed, given its views on patient safety Merck Serono asked Roche in a letter of 3 February, whether these data had been included in Roche promotional materials to ensure accurate reflection of the evidence regarding bevacizumab in the RAS mutant population in compliance with Clause 7.2. To date no reply to this point had been received.

Merck Serono submitted that the bullet point was included to provide full disclosure of the study results in both the RAS wild-type and mutant population. No claims for efficacy were made and Merck Serono submitted that that the bullet point was not misleading, did not encourage inappropriate use of cetuximab or endanger patient safety. Accordingly Merck Serono refuted a breach of Clauses 7.2, 7.3, 7.10 or 22.2. Merck Serono submitted that as Clause 22.2 related to non-interventional studies it was not sure why Roche alleged a breach of that clause.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

Merck Serono submitted that the importance of the FIRE-3 results had also been reflected by the Cancer Drugs Fund recent inclusion of Erbitux and FOLFIRI as an allowed therapy for the treatment of first-line RAS wild-type metastatic colorectal cancer. The results of FIRE-3, an increase of 7.5 months survival, was one of the largest seen in any oncology study, the clinical significance of which had been widely recognised including by the European Medicines Agency (EMA) with the change in marketing authorisation.

5 Overall

This quotation was an accurate reflection of the investigator's views, did not encourage inappropriate use of cetuximab and was therefore not in breach of Clauses 7.2, 7.10, 10.2 or 22.2. As noted above, Clause 22.2 related to non-interventional studies.

In summary, Merck Serono submitted that the press release was an accurate reflection of the results of the FIRE-3 study presented at ESMO. The data were regarded as an important advance in the treatment of first-line RAS wild-type metastatic colorectal cancer. That the data were generally accepted was evidenced by the change in marketing authorisation and inclusion of the regimen in the National Cancer Drugs Fund list. The claims were not misleading, unbalanced nor did they put patient safety at risk as alleged and accordingly Merck Serono submitted that it had not breached Clauses 9.1 or 2.

* * * * *

In response to requests for further information, Merck Serono submitted that the change of the Erbitux licensed indication to all RAS wild-type metastatic colorectal cancer occurred in December 2013 and reflected the narrowing of the eligible licensed population from KRAS wild-type. Merck

Serono also provided a copy of the slides presented at the ASCO meeting, 2013 and highlighted a slide detailing the treatment duration. The median time of treatment in the FOLFIRI + cetuximab and FOLFIRI + bevacizumab arms was 4.8 months and 5.3 months respectively. Merck Serono submitted that the proportion of patients initially treated with FOLFIRI + cetuximab and which subsequently received bevacizumab as second-line treatment was similar to the proportion of patients which initially received FOLFIRI + bevacizumab and then received an anti-EGFR mAB such as cetuximab as second-line therapy. Merck Serono submitted that in both groups over 60% of patients received oxaliplatin as second-line treatment and thus the treatment arms were considered balanced. Merck Serono highlighted a slide from a presentation by Modest *et al* which gave further detail.

PANEL RULING

The Panel noted that the press release was dated 28 September 2013 and that Roche cited Clauses 7.2, 7.3, 7.4, 7.10, 10.2 , 22.2, 9.1 and 2 of the 2012 Second Edition (amended) Code. The 2014 Code came into operation on 1 January 2014 with a transition period until 30 April 2014 for newly introduced requirements. The clauses cited were not the same in the 2014 and Second 2012 Edition (amended) Codes, thus the Panel used the Second 2012 Edition (amended) Code.

The Panel noted that both parties had referred in general terms to UK promotional material. Roche, which as the complainant bore the burden of proof on the balance of probabilities, had not clearly identified any such material or made detailed allegations. The Panel decided to make its ruling upon the press release noting that any such rulings would apply to closely similar materials.

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study'

The Panel noted that the press release was dated 28 September 2013 and was headed 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'. Below, in slightly smaller text, were two bullet points; 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 to 33.1 months (p=0.011) in mCRC patients with RAS wild-type tumours receiving 1st line Erbitux plus FOLFIRI compared with patients receiving bevacizumab plus FOLFIRI' and 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'.

Text beneath referred to the phase III head-to-head trial which showed a 'clinically relevant improvement from Erbitux (cetuximab) plus FOLFIRI vs bevacizumab plus FOLFIRI as first-line treatment in metastatic colorectal cancer (mCRC) in patients with RAS wild-type tumours'.

The Panel noted that the FIRE-3 study was a multicentre randomised phase III trial investigating 5-FU, folinic acid and irinotecan (FOLFIRI) plus cetuximab versus FOLFIRI plus bevacizumab in first-line treatment of metastatic colorectal cancer (mCRC). The study failed to meet its primary endpoint of overall response rate (ORR). Secondary endpoints included median progression free survival (PFS) and median overall survival.

The FIRE-3 study principal investigator gave the FIRE-3 oral presentation at the European Cancer Congress, the summary of his presentation stated 'OS was markedly superior (Δ = 7.5 months, HR 0.70) in all RAS wild-type patients receiving first-line therapy with cetuximab (p=0.011)'. The presentation concluded that upfront determination of RAS (KRAS and NRAS) mutation status appeared to be highly recommendable in patients with metastatic disease and concluded that 'Patients with all-RAS wild-type tumours have a clinically relevant survival benefit when first-line treatment with cetuximab is offered'.

The Panel noted that in its general comments Roche queried the degree to which the first-line treatment was responsible for any overall survival difference demonstrated as the Kaplan-Meier curves of overall survival representing the different study arms presented at ASCO 2013 did not begin to separate until the 15-18 month time point whereas the median time to first progression was approximately 10 months in both arms (10.0 and 10.3 months) and the reported median duration of first-line treatment was significantly shorter than this in both arms. The Panel noted that Merck Serono did not provide much detail in response to Roche's statement other than highlighting the median duration of treatment in the FOLFIRI + cetuximab and FOLFIRI + bevacizumab arms which was 4.8 months and 5.3 months respectively. The Panel further noted that only 15.2% of patients in the FOLFIRI + cetuximab treatment arm and 11.4% in the FOLFIRI + bevacizumab treatment arm had received Anti-EGFR mAB treatment such as cetuximab as part of their second-line treatment. The Panel did not consider this point further as there was no specific allegation.

The Panel noted Roche's allegation that the overall survival statement in the press release heading was misleading because the fact that the FIRE-3 study failed to reach its primary endpoint was not prominently presented within the press release and the full nature of the study results were not represented in the heading or summary bullet points. The Panel disagreed with Merck Serono's decision that as the lack of difference in ORR and PFS had previously been reported in the ASCO press release and as there was no change in these endpoints it was not considered appropriate to include them in the heading. It was a well established principal of the Code that each claim had to be capable of standing alone. The Panel considered that the heading, 'Merck Serono's Erbitux Significantly Extends Survival to 7.5 Months in mCRC Wild-Type Patients When Compared with Bevacizumab:

New Analysis of FIRE-3 AIO Study', was not a fair reflection of the overall data; it had not been placed within context of the study's primary outcome. The reference to the study's failure to meet its primary endpoint of objective response rate based on investigators' read in patients with KRAS EXON 2 wild-type tumours appeared in the third paragraph on page 2 and was insufficient to counter the heading. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the secondary endpoint findings. The heading was therefore misleading as alleged and the Panel ruled a breach of Clauses 7.2. This ruling was appealed.

2 First bullet point in press release: 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival from 25.6 months to 33.1 months (p=0.011) …'

The Panel noted Roche's allegation that the first bullet point 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 to 33.1 months (p=0.011) in mCRC patients with RAS wild-type tumours receiving 1st line Erbitux plus FOLFIRI compared with patients receiving bevacizumab plus FOLFIRI' similarly failed to set this finding clearly in the context of the overall study. The Panel considered that its general comments above in relation to the heading (point 1 above) were relevant here. The sub-group analyses had not been placed in context of the study's failure to achieve its primary endpoint. In addition, the Panel was concerned that the press release did not make it clear at the outset that the data was from a pre-planned exploratory analysis. The only reference to this was on the second page of the press release and there was no explanation that no confirmatory clinical conclusions could be drawn from such an analysis. In the opinion of the Panel the press release invited the reader to draw such conclusions. Exploratory analyses should not be used as the basis for a robust comparison of medicines. The material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The Panel considered that the bullet point was misleading as alleged and ruled a breach of Clause 7.2. This ruling was appealed.

The Panel noted Roche's submission that during inter-company dialogue Merck Serono was unable to comment on its statistical concerns about the analyses and directed it to the study sponsor. Roche alleged that Merck Serono was therefore unable to substantiate the sub-group analysis and was thus in breach of Clause 7.4. The Panel noted Merck Serono's submission that it disagreed that Roche's concerns were valid and directed it to the AIO investigators who would be best placed to assist with its query. The Panel noted that Roche had not alleged a breach of Clause 7.5 which required substantiation for any information, claim and comparison to be provided as soon as possible and certainly within 10 working days. The Panel was concerned that Merck Serono did not comment on the statistical validity of the sub-group analysis or contact the study organisers and provide feedback to Roche during inter-company dialogue. Nonetheless Roche had alleged a breach of Clause 7.4 which required that information, claims and comparisons be capable of substantiation. Merck Serono submitted that the bullet point in question was supported by the data presented at ESMO. However, the Panel noted that the ESMO presentation did not appear to cover statistical analysis of the sub-group although the abstract made it clear that the analysis was pre-planned. The Panel however did not have any accompanying transcript.

The Panel noted Roche's allegation that the sub-group analysis needed to be accounted for statistically to avoid bias from multiple analyses. On balance, and on this very narrow point, the Panel ruled that the bullet point in question was not capable of substantiation. A breach of Clause 7.4 was ruled. This ruling was appealed.

3 Second bullet point: 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'

The Panel noted Roche's allegation that the second bullet point 'In the group with any RAS mutations, patients who received Erbitux in first-line reached a median OS of 20.3 months vs 20.6 months in the group that was treated with bevacizumab in 1st Line (p=0.60)' suggested that there was no difference between the arms with respect to overall survival in the sub-group of patients with RAS mutant mCRC. The Panel noted Roche's submission that cetuximab was not licensed for RAS mutant mCRC in Europe and was contraindicated in the treatment of RAS mutant mCRC with certain chemotherapy combinations. Roche was concerned that neither this licence restriction nor the licensed indication of cetuximab were mentioned in the press release which was alleged to be misleading and not to encourage the rational use of cetuximab.

The Panel considered that the comparison was misleading as it was not clear that it was based on a pooled analysis of two different populations of patients with RAS mutations from two different time points. The Panel ruled a breach of Clauses 7.2 and 7.3 as it considered that the context of the comparison was not clear and it was therefore misleading. This ruling was accepted.

The Panel disagreed with Merck Serono's submission that the comparison made no efficacy claims for cetuximab. The Panel considered that the overall survival comparison of cetuximab with bevacizumab in patients with any RAS mutations was misleading as it implied that like bevacizumab, cetuximab was licensed for the treatment of RAS mutant mCRC which was not so. It was only licensed for EGFR expressing RAS wild-type metastatic colorectal cancer. [At the time of the press release Erbitux was only licensed for EGFR expressing KRAS wild-type metastatic colorectal cancer]. In the Panel's view, the failure of Merck Serono to place the bullet point within the context of cetuximab's licensed indication and the failure to mention relevant contraindications was misleading and did not encourage the rational use of cetuximab and breaches of Clause 7.2 and 7.10

were ruled. A breach of Clause 7.3 was also ruled as the comparison was misleading. These rulings were accepted. The Panel noted that Roche made reference to Clause 3.2 but no allegation was made and thus the Panel made no ruling in this regard.

The Panel noted that Merck Serono was unsure why Roche had raised Clause 22.2 as it related to non-interventional studies. This was so in the 2014 Code. However, both the allegation and response appeared to relate to Clause 22.2 of the 2012 Second Edition (amended) Code which required, *inter alia*, that information about prescription only medicines which was made available to the public either directly or indirectly, must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. The Panel noted Merck Serono's submission that the press release had been sent to forty medical and pharmaceutical titles, twenty-three health journalists at national print and online titles and sixteen freelance health journalists. The Panel noted its rulings above in relation to the misleading statements made about Erbitux and considered that in relation to the matters discussed above the press release was not factual and had not presented information about Erbitux in a balanced way contrary to Clause 22.2. A breach of Clause 22.2 was ruled. This ruling was accepted.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

The Panel noted Roche's concern regarding the statement 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies' which was referenced to the FIRE-3 principal investigator, and was made in reference the new median survival data. The supplementary information to Clause 10.2 stated that any quotation used in promotional material must comply with the Code.

The Panel noted its comments and rulings at points 1 and 2 above with regard to the data from the FIRE-3 study showing a 7.5 month increase in median overall survival when using Erbitux plus FOLFIRI as compared with using bevacizumab plus FOLFIRI in metastatic colorectal cancer. The Panel considered that the quotation was misleading as within the context of the median survival data it applied disproportionate weight to the results thereby exaggerating Erbitux's properties and consequently it did not encourage the product's rational use. The Panel thus ruled breaches of Clauses 7.2, 7.10 and 10.2. The Panel noted its comments above with regard to Clause 22.2 and similarly ruled a breach of that clause. These rulings were appealed.

5 Overall

The Panel noted all of its rulings of breaches of the Code above and considered that Merck Serono had failed to maintain high standards. A breach of Clause 9.1 was ruled. This ruling was appealed.

With regard to Clause 2, the Panel noted that it was used as a sign of particular censure and reserved for such use. The supplementary information to Clause 2 gave examples including prejudicing patient safety. The Panel noted that Roche had referred to patient safety. The Panel noted its rulings of breaches of the Code above. The Panel considered that it was very important that press releases about sensitive issues such as survival in cancer were fair, factual and not misleading. The press release had failed to reflect the study's primary endpoint and the product's licensed indications. In particular the headline claim about survival had been ruled in breach of the Code. The Panel considered that on balance the circumstances warranted such a ruling and a breach of Clause 2 was ruled. This ruling was appealed.

APPEAL BY MERCK SERONO

Prior to laying out the points of appeal, Merck Serono noted that setting the context within which the press statement was released (in terms of the licence for Erbitux (cetuximab) and the evolving scientific knowledge regarding RAS mutations and their relation to efficacy) would be helpful to the Appeal Board.

Merck Serono noted that one of the principal complaints by Roche of the press release at issue related to the secondary endpoint of median overall survival (OS) and comparison of that endpoint in a subset of patients in the cetuximab treatment arm and patients in the bevacizumab treatment arm; the outcome of 33.1 vs 25.6 months (p=0.011) favoured cetuximab.

Merck Serono noted that the primary endpoint of the study was the overall objective response rate (ORR) which did not show any statistically significant difference between treatment arms. Due to the non-significance of the primary endpoint Roche alleged that the comparison was in effect misleading; the Panel agreed. Whilst this complaint had been going through the complaint's procedure, this comparison (and other associated data) had also been reviewed by the EMA, and following a positive opinion on 26 June 2014 these data were now incorporated into the cetuximab SPC.

Merck Serono submitted that the information promulgated in the press statement was therefore capable of withstanding detailed scrutiny. Given that these data were now being incorporated into the licence for cetuximab, it was accurate and did not mislead, and this was the basis for the appeal.

Current Licence

'For the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer

- In combination with irinotecan-based chemotherapy
- In first-line in combination with FOLFOX
- As a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.'

Merck Serono submitted that FOLFOX and FOLFIRI were two principal chemotherapy regimens used in

the treatment of metastatic colorectal cancer (mCRC) upon which biological agents such as cetuximab or bevacizumab might be added with a view to improving outcomes compared with chemotherapy alone. Both these chemotherapy regimens were acceptable within the licence for use with cetuximab. As the chemotherapy background had not changed within the licence, for clarity, discussion of changes to the licensed indication for cetuximab would be limited to discussion of the RAS tumour (mCRC) status, since this was the key element of change within the licence, and also key in understanding the appeal.

Merck Serono submitted that when cetuximab was first licensed in 2004 it was indicated for the treatment of EGFR-expressing mCRC. Subsequently the licence had been specifically amended to inform further the patients who were appropriate for treatment with cetuximab, and importantly identifying those patients (based upon analysis of tumour biomarkers) who were highly unlikely to respond to treatment, and as such should not have treatment with cetuximab initiated.

KRAS licence update

Merck Serono submitted that the first change to the licence in this respect occurred in 2008 when it became increasingly clear that the activity of EGFR targeting therapies was restricted to patients who did not express activating mutations of KRAS proteins (see below for details), hence only patients with proven KRAS wild-type, [ie non mutant] tumour status should be considered for treatment with cetuximab. This licence indication remained unchanged until December 2013, and hence when the press statement was released (28 September 2013) was the licensed indication for cetuximab (SPC dated September 2008).

RAS licence update

Merck Serono submitted that a second change to the licence occurred in December 2013 with the reporting of new studies, in particular OPUS, and followed identification of other mutations beyond those originally examined (KRAS EXON 2) to include mutations in EXONS 3, and 4 of genes expressing KRAS activity, and also in EXONS 2, 3 and 4 of genes expressing NRAS activity. Analysis had indicated that in patients with mCRC expressing mutations of either (or both) KRAS and NRAS (EXONS 2, 3 and 4) were again highly unlikely to respond to treatment with EGFR targeted therapies.

Merck Serono submitted that after December 2013, the licence for cetuximab was therefore restricted to patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer, ie, no mutations within the loci described immediately above. It was the outcomes of this patient sub-group from within the FIRE-3 study that was reported upon within the press release at issue, and in particular it was stated that the median OS in mCRC RAS wild-type patients receiving first-line FOLFIRI plus cetuximab (FOLFIRI/cetuximab) was 33.1 months compared with 25.6 months in patients receiving first-line FOLFIRI plus bevacizumab (FOLFIRI/bevacizumab). This RAS wild-type patient population was (and still was) within licence since KRAS wild-type (as stipulated within the licence at that time) was a broader patient population; ie RAS wild-type was a subset within the KRAS wild-type population (SPC dated December 2013).

Merck Serono submitted that the results of the FIRE-3 study and analyses of the subset of patients with RAS wild-type status has been reviewed by the EMA, following which a positive opinion from the CHMP on 26 June 2014 was concluded and the licence for cetuximab was being updated to include these efficacy data (Updated SPC; CHMP positive opinion dated 26 June 2014).

Mechanism of action of EGFR targeted therapies

Merck Serono submitted that cetuximab was a chimeric monoclonal immunoglobulin G1 (IgG1) antibody directed at the epidermal growth factor receptor (EGFR). EGFR signalling pathways were involved in, amongst other activities, the control of cell survival, cell cycle progression, cell migration and invasion/metastasis. Cetuximab bound to the EGFR with a higher affinity than endogenous ligands, thus effectively blocking the receptor and subsequent intra-cellular signalling, and leading also to internalisation of the EGFR. Cetuximab also targeted cytotoxic immune effector cells towards EGFR-expressing tumour cells; an example of antibody dependent cell-mediated cytotoxicity (ADCC). Cetuximab therefore led to inhibition of intra-cellular signalling associated with EGFR activation and hence interfered with cell function, an action which ultimately could be lethal to that cell, as well as initiating ADCC.

KRAS and RAS proteins

Merck Serono submitted that RAS proteins were a ubiquitous group of intra-cellular proteins implicated in a number of down-stream signalling processes which normally controlled cell cycling; as such they were also known as proto-oncogenes. Under normal circumstances these proteins could be 'activated' following stimulation of EGF-receptors; their subsequent and controlled 'deactivation' allowed for regulated activity.

Merck Serono submitted that RAS proteins might also be 'activated' via mutations of the RAS genes leading to unregulated activity which bypassed the normal EGF-receptor activation (and subsequent deactivation) sequence. Since activation of RAS proteins via these gene mutations were independent of the EGFR signalling pathway it followed that a therapy targeting an EGF- receptor, such as cetuximab, would be highly unlikely to be effective against a tumour cell with mutated RAS onco-genes. For clarity in the document, the RAS protein family could be divided broadly into two principal groups, NRAS, KRAS, (and a third group HRAS not discussed further here), which were collectively known as RAS proteins. The nomenclature for the protein groups was based upon the *in vitro* models from which they were first identified;

RAS **Ra**t **s**arcoma proto-oncogene
KRAS **K**irsten **ra**t **s**arcoma 2 viral oncogene homolog
NRAS **N**eurobalstoma **RAS** viral oncogene homolog
HRAS v-Ha-**RAS** Harvey rat.

Merck Serono submitted that since cetuximab was first licensed (and another EGFR targeting therapy, panitumumab also gained its licence) there had been a growing awareness of the patient population for whom, because of identifiable tumour RAS status, EGFR targeting therapies might be an appropriate treatment, and also those patients in whom such treatment should not be initiated because of the likelihood that the treatment would not be effective ie those patients whose tumours would be predicted as highly likely to be resistant to cetuximab.

Merck Serono submitted that scientific knowledge had evolved over the past few years, along with RAS testing, that now enabled these distinct patients populations (those with RAS mutations, and those without mutations ie RAS wild-type) to be identified with some certainty such that patients did not receive an EGFR targeted therapy inappropriately. This was not the case at the start of many of the clinical trials involving EGFR targeted therapies, some of which had only recently reported results (eg FIRE-3), and indeed others which had only reported interim results (eg CALGB 80405). Such trials had included initially patients in whom mCRC KRAS status was unknown; subsequently, with the awareness of the importance of KRAS testing the entry criteria for these studies was amended to exclude patients with known KRAS mutations.

Investigators therefore had become aware (retrospectively) that some of the patients in the cetuximab treatment arm would have had tumours which based upon KRAS testing would have been resistant to that treatment and hence those patients would not have been likely to derive any additional benefit over the use of chemotherapy alone. Conversely there would also be patients for whom an EGFR targeted therapy was an appropriate option as an add on to chemotherapy and it would be important to report such patients separately from those predicted to be resistant in order to define firstly the appropriate patient population for EGFR targeted therapy, and secondly to determine the potential benefit of such treatment. Furthermore, additional mutations of KRAS and NRAS had been identified that also predicted likely resistance to cetuximab treatment, again increasing the necessity to correctly identify patients prior to initiation of cetuximab treatment, and also to report the outcomes by different RAS mutation status rather than by broad populations.

Evolution of RAS testing

Merck Serono submitted that initial RAS testing sought to identify mutations of the KRAS group at genetic 'hotspots'. The most frequently involved was at EXON 2, (codons 12 and 13) and accounted for most of the known genetic mutations of the RAS system. Patients with KRAS mutations at these sites were then excluded from study entry via protocol amendments. Such amendments occurred in several studies including FIRE-3.

Additional mutations were subsequently identified (at a much lower frequency) at KRAS EXONS 3 and 4, and also at NRAS EXONS 2, 3 and 4 which also predicted the likelihood of resistance to cetuximab. Consequently, in reporting the results of such studies, (via analyses of the primary endpoint in the intention-to-treat (ITT) population which would contain a subset of patients with RAS mutations making them resistant to cetuximab therapy) care should therefore be exercised in drawing absolute clinical conclusions from such analyses, even though the statistical methodology was correct.

Post-hoc analysis of patient subsets from studies such as OPUS and CRYSTAL had enabled a more informed understanding of the potential benefit (or otherwise) of using an EGFR targeted therapy, based upon analysis of RAS mutations.

The Phase II OPUS study which investigated first-line use of cetuximab plus FOLFOX4 vs FOLFOX4 alone had indicated that for the KRAS wild-type population (within licence until December 2013) the median OS was 22.8 months vs 18.5 months in favour of cetuximab compared with chemotherapy alone (HR 0.855; 95% CI 0.599, 1.219 p=0.3854 not significant). For the KRAS mutant population median OS was 13.4 months vs 17.5 months in favour of FOLFOX4 alone (HR 1.29; 95% CI 0.873, 1.902 p=0.2) ie a negative effect of cetuximab when combined with FOLFOX4 in this defined (KRAS mutant) patient population who were highly likely to be resistant to EGFR targeting therapies.

Although patient numbers were small (FOLFOX4/ cetuximab KRAS wild-type n=82: FOLFOX4/ cetuximab KRAS mutant n=77) and p values did not achieve statistical significance, the directional outcomes of these exploratory analysis supported a licence change for cetuximab in 2008 which restricted use to patients with KRAS wild-type status (SPC September 2008).

Merck Serono submitted that exploratory analyses of other subsets of patients within OPUS had further supported this restriction; in patients with any RAS mutation and who received FOLFOX4/ cetuximab median OS was 13.5 months compared with 17.8 months with FOLFOX4 alone; ie a negative effect for patients with RAS mutations receiving cetuximab plus FOLFOX4 (P=0.157). Although not significant statistically, the tumour cell biology and mechanism of action for EGFR targeted therapies provided compelling reasons for not treating patients with RAS mutations with cetuximab (SPC December 2013).

Merck Serono submitted that the converse is also true, ie exploratory analyses of subsets of patients from these studies had also helped identify patients for which treatment outcomes were improved. In the CRYSTAL study which compared cetuximab with FOLFIRI to FOLFIRI alone, a positive outcome was noted in the analysis of patients with KRAS wild-type status receiving cetuximab as an add-on compared with FOLFIRI alone; 23.5 vs 20.0 months HR 0.8;

95% CI 0.67, 0.95 p=0.0093. No such benefit was seen in the KRAS mutation population. Importantly within the KRAS wild-type population receiving FOLFIRI/cetuximab the PFS and ORR were also improved compared with those patients receiving FOLFIRI alone, both achieving statistical significance p=0.0012 and <0.0001 respectively (see SPC June 2009).

Merck Serono submitted that the KRAS wild-type population in CYRSTAL also included some patients with other RAS mutations and who were consequently resistant to cetuximab treatment. Further analysis of additional RAS mutations (beyond KRAS EXON 2) indicated that in the RAS wild-type population, those patients who had received cetuximab plus FOLFIRI had a median OS of 28.4 vs 20.2 months compared with FOLFIRI alone, HR 0.69; 95% CI 0.54, 0.88 p=0.0024. For those patients with any RAS mutation there was no statistical difference between treatment arms: median OS 16.4 vs 17.7 HR 1.05 95% CI 0.86, 1.28 p=0.64. Again supporting this improvement in overall survival for the RAS wild-type subset of patients, the data for PFS an ORR also achieved statistical significance p=0.0024 and <0.0001 respectively (updated SPC June 2014).

Merck Serono submitted that although exploratory, the analyses of patient subsets based on RAS status (mutation or wild-type) nevertheless allowed a rationale review of outcomes based upon biomarkers which could be used for appropriate patient selection for treatment (or otherwise) with EGFR targeted therapies. It was also obvious that exclusion of patients (for whom resistance to therapy was highly likely) would improve the outcome of an analysis for EGFR targeted therapies. Under these circumstances, and in particular as the licence for cetuximab had been amended to exclude patients with RAS mutations from treatment, these types of analyses [x patient subsets] of results from older clinical trials that were now being reported would continue, and also would yield important information about treatment outcomes.

Merck Serono submitted that dismissing such exploratory analyses on the basis of purely statistical grounds would not be appropriate clinically, and could affect patient care. In purely statistical terms the construct hypothesis had changed such that the comparison from the ITT population were not strictly of clinical relevance today since the ITT population included patients with resistance to EGFR targeted therapies. Of relevance was the comparison of one treatment used for appropriate patients against another also being used for appropriate patients. It was within this context that the comparison of cetuximab with bevazicumab was made in the press statement.

Analysis of FIRE-3 and update to the licence for cetuximab

Merck Serono submitted that FIRE-3 was an open label, randomised (1:1), phase III study which investigated the efficacy of FOLFIRI in combination with cetuximab vs bevacizumab in first-line treatment of mCRC. The study was initiated in 2007 and a 'cut-off' date was April 2013. Initially unselected mCRC patients were enrolled, and following an amendment in October 2008, KRAS EXON 2 wild-type patients only were included; this latter group forming the ITT population (n=592). Other amendments to the study were considered minor. The study was conducted in Germany and Austria in 150 active sites.

Second-line therapy recommended after FOLFIRI + cetuximab was FOLFOX (plus bevacizumab 'if needed') and after FOLFIRI + bevacizumab: irinotecan + cetuximab. The primary endpoint of the ITT analysis was ORR using investigator evaluation (RECIST 1.0); these occurred after 6 and 12 weeks, and thereafter every 10 weeks. Secondary endpoints included PFS and median OS. Where tumour samples were available, the mutation status of KRAS EXON 2 (codons 12 and 13), EXON 3 (codon 61) and EXON 4 (codon 146), and NRAS EXON 2 (codons 12 and 13), EXON 3 (codons 59 and 61), and EXON 4 (codons 117 and 146) were analysed. In total 753 patients were enrolled, of which 113 patients were subsequently identified with KRAS EXON 2 mutations. From the ITT population of 592 KRAS EXON 2 wild-type patients, 407 (69%) had had tissue samples of the tumour collected and suitable for expanded RAS analysis (the RAS evaluable population). Of this RAS evaluable population 342 (FOLFIRI/cetuximab n=171, FOLFIRI/bevacizumab n=171) were RAS wild-type and 65 had 'new' RAS mutations. The 'new' RAS mutations plus the 113 KRAS EXON 2 mutations collectively formed the RAS mutation population (n=178; 92 with FOLFIRI/cetuximab and 86 with FOLFIRI/bevacizumab). Results for the ITT KRAS EXON 2 wild-type, RAS wild-type and RAS mutation populations were presented below (updated SPC June 2014);

KRAS wild-type ITT population (n=592)

ORR (primary endpoint) cetuximab + FOLFIRI 62%, bevacizumab + FOLFIRI 58%; p=0.183: Primary endpoint not met

PFS (secondary endpoint) cetuximab + FOLFIRI 10 months, bevacizumab + FOLFIRI 10.3 months: p=0.547

Median OS (secondary endpoint) cetuximab + FOLFIRI 28.7 months, bev + FOLFIRI 25 months

HR=0.77 p=0.017, Δ=3.7 months in favour of cetuximab arm

RAS wild-type population (n=342)

OORR: FOLFIRI/cetuximab 65.5%, FOLFIRI/bevacizumab 59.6% p=0.32 not significant

PFS: FOLFIRI/cetuximab 10.4 months, FOLFIRI/bevacizumab 10.2 months p=0.54 not significant

Median OS: FOLFIRI/cetuximab 33.1 months, FOLFIRI/bevacizumab 25.6 months p=0.011

HR 0.7 (95%CI 0.53 – 0.92) Δ=7.5 months in favour of cetuximab arm

RAS mutation population (n=178)

(RAS mutations =KRAS EXON 2 mutations (n=113) plus 'new' RAS mutations (n=65)

OORR: FOLFIRI/cetuximab 38.o%, FOLFIRI/ bevacizumab 51.2% P=0.097 (favours bevacizumab)

PFS: FOLFIRI/cetuximab 7.5 months, FOLFIRI/ bevacizumab 10.1 months p=0.085

HR 1.31 Δ=2.6 months in favour of bevacizumab arm

Median OS; FOLFIRI/cetuximab 20.3 months, FOLFIRI/bevacizumab 20.6 months p=0.6

Difference not significant

Discussion of results of FIRE-3.

Merck Serono submitted that though the primary endpoint of the ITT population was not significant in terms of ORR, pre-planned exploratory analysis of previously identified patient sub-types was performed. The cetuximab arm of this ITT population with KRAS EXON 2 wild-type status confirmed would still include a portion of patients who had mutations at loci other than KRAS EXON 2 (65 such patients were identified). Exclusion of these patients from analysis was appropriate since they were predicted to be resistant to treatment on the basis of tumour biology and the mechanism of action of cetuximab. Analysis of the RAS wild-type population would therefore yield a more precise view of the benefit of cetuximab when added to FOLFIRI in an appropriately defined population. This was a sensible course of action to pursue in order to help inform clinical practice.

Merck Serono submitted that the results for the overall ITT population indicated a small but statistically significant difference of 3.7 months in terms of median OS for the cetuximab arm compared with the bevacizumab arm. This population contained patients resistant to cetuximab (KRAS and NRAS mutations), hence removing them and then reanalysing the remaining patients (RAS wild-type) would increase this survival difference, ie to a Δ of 7.5 months in favour of cetuximab.

Merck Serono submitted that this was not a chance finding, but followed analysis of the data based upon testing for RAS mutations, and was reflective of tumour biology and removal of patients likely to be resistant to EGFR therapy. This was logical to do as it informs selection of appropriate therapy for individual patients.

Merck Serono submitted that it would now be wrong to initiate treatment with cetuximab in patients without knowledge of their RAS status as clinical studies had shown unequivocally that patients with RAS mutational status did not respond to cetuximab (and the licence had been updated to reflect this). Under such circumstances patients would have a negative effect from receiving cetuximab in terms of gaining no efficacy benefit, but experiencing side effects of treatment. This was not however known when FIRE-3, and other studies in mCRC were initiated, and as this new information about potential response/resistance had become available it was important to report data for patients within these studies by RAS status so that patients in whom cetuximab had been appropriately administered could be identified and the outcomes scrutinised.

Merck Serono submitted that there were however several key questions with regard to the validity of the survival data for RAS wild-type patients in the FIRE-3 study; Why if there was a survival advantage for cetuximab, was there no difference between treatment arms for PFS? Why did the Kalpan-Meier curves only start to separate long after cessation of first-line treatment? Responses addressing these important questions were submitted to the EMA when updating the licence for cetuximab in respect of the CRYSTAL and FIRE-3 efficacy data.

Merck Serono submitted that it could be considered surprising that a survival advantage was seen in FIRE-3 for patients with RAS wild-type status when there was no real difference in PFS between the treatment arms. In patients with RAS mutant and wild-type status, post progression survival seems to be longer in the cetuximab treated arm. In the case of RAS mutations, due to the fact that these tumours were highly likely to be resistant to EGFR targeted therapies, improved post progression survival could not be due to post progression effects of cetuximab first-line.

Merck Serono submitted that this was similar to findings noted in the PEAK study which investigated panitumumb (another EGFR targeted therapy) or bevacizumb as add on to FOLFOX6; both median OS and survival post-progression were superior in the EGFR targeted treatment arm when compared with bevacizumab. This might be related either to some other actions of EGFR targeted therapies, or possibly due to some inherent property of bevacizumab (Schwatzberg *et al* 2014).

Merck Serono submitted that recently the results of study ML18147 (2013) which investigated prolonged treatment with bevacizumab as add-on to next-line chemotherapy compared with next-line chemotherapy alone in patients failing first-line chemotherapy + bevacizumab in mCRC. Patients with progressive disease on first-line therapy within 3 months, or bevacizumab administered for less than 3 months were excluded from the study. The results reported improvement in overall survival for the prolonged treatment group, HR 0.8 (p=0.006) (Bennouna *et al* 2013).

Merck Serono submitted that as no likely differences in second-line treatment were reported from the FIRE-3 study the prolonged post-progression survival in the cetuximab arm might be related to stopping bevacizumab at time of progression. Theoretically, cessation of bevacizumab might lead to tumour neoangiogenesis and hence an enhanced tumour progression rate in some patients receiving bevacizumab. Such a theory would fit reasonably well with the ML18147 study, and might also help to explain the positive outcome of prolonged

bevacizumab treatment in that study. Such a theory might also help explain the late separation of the Kaplan-Meier curve in respect of overall survival in the FIRE-3 study whereby neoangiogenesis following cessation of treatment in the bevacizumab arm led to a faster rate of tumour progression, the outcome of which was expressed ultimately within the survival curves.

Merck Serono submitted that in addressing the issue of no significant differences between the primary analysis of ORR in the ITT population n=592, which was 62% for FOLFIRI/cetuximab and 58% FOLFIRI/bevacizumab, (difference not significant), further analysis had also been performed. The ITT population consisted of patients with KRAS wild-type status, and that population included some patients also with RAS wild-type mutations which would impart resistance to cetuximab therapy. These patients should therefore be excluded for mechanistic reasons as explained previously. The ORR was also measured by investigators within the open label FIRE-3 study using Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 (a set of rules to define when cancer patients improved ('respond'), stayed the same ('stable') or worsened ('progression') during treatment). ORR consisted of those patients with a complete plus partial response to therapy. An independent evaluation of tumour response had also been performed, and by reviewers blinded to treatment and patient data using RECIST 1.1. Results of this independent evaluation of ORR had recently been reported (Heinemann *et al* 2014), and might help explain the survival advantage accrued to the cetuximab treatment arm in FIRE-3 in patients with RAS wild-type status.

Merck Serono submitted that the independent review of scans of tumour response were made available to blinded reviewers who assessed early tumour shrinkage (ETS: expressed as a greater than 20% reduction in size at week 6), depth of response (DpR: expressed as the largest measured reduction in tumour size throughout the treatment cycle) and ORR (complete plus partial response). All results favoured FOLFIRI/cetuximab;

	FOLFIRI/ cetuximab	**FOLFIRI/ bevacizumab**	**p value**
ORR	72.5%	55.5%	0.0063
ETS	69.2%	47.4%	0.0006
mDpR	48.6%	32.2%	0.003

Merck Serono submitted that these results seemed to indicate that FOLFIRI/cetuximab led to an earlier and deeper tumour response compared with FOLFIRI/bevacizumab, and could also help to explain the improved survival advantage of 7.5 months seen with the cetuximab treatment arm in FIRE-3 in the subset of patients with RAS wild-type status.

Merck Serono submitted that therefore that the results of the analysis of FIRE-3 subsets were based upon mechanistic rationale, and included patients for whom cetuximab was an appropriate treatment, whilst also demonstrating in those patients for whom resistance was predicted, either no clinical benefit or indeed a negative effect as an add-on to chemotherapy.

Merck Serono submitted that also rational explanations for improved survival in the cetuximab treatment arm in those patients for whom cetuximab therapy was most appropriate ie those with no RAS mutations.

Merck Serono submitted that other clinical studies were also due to report; in particular the CALGB 80405 study. Interim results of patients with KRAS wild-type status had been presented at ASCO in June of this year. The top-line results did not repeat the observations in patients receiving FOLFIRI/cetuximab as per the FIRE-3 study. During the assessment by the EMA of the CRYSTAL and FIRE-3 data, the CALGB study and interim results were noted. Also noted was the fact the analysis of the results by RAS status had not yet occurred and these analyses were required in order to evaluate properly the results.

Merck Serono submitted that within this particular framework the CHMP had accepted the proposed

Variable/statistic	**RAS wild-type Cetuximab plus FOLFIRI (N=171)**	**Bevacizumab plus FOLFIRI (N=171)**	**RAS mutant Cetuximab plus FOLFIRI (N=92)**	**Bevacizumab plus FOLFIRI (N=86)**
OS				
months, median	33.1	25.6	20.3	20.6
(95% CI)	(24.5, 39.4)	(22.7, 28.6)	(16.4,23.4)	(17.0, 26.7)
Hazard Ratio (95% CI)	0.70 (0.53, 0.92)		1.09 (0.78, 1.52)	
p-value	0.011		0.60	
PFS				
months, median	10.4	10.2	7.5	10.1
(95% CI)	(9.5, 12.2)	(9.3, 11.5)	(6.1, 9.0)	(8.9, 12.2)
Hazard Ratio (95% CI)	0.93 (0.74, 1.17)		1.31 (0.96, 1.78)	
p-value	0.54		0.085	
ORR				
%	65.5	59.6	38.0	51.2
(95% CI)	(57.9, 72.6)	(51.9, 67.1)	(28.1, 48.8)	(40.1, 62.1)
Odds Ratio (95% CI)		1.28 (0.83, 1.99)		0.59 (0.32, 1.06)
p-value		0.32		0. 097

OS = overall survival time; PFS = progression-free survival time; ORR = objective response rate

updates to the SPC in terms of the benefit-risk for the efficacy data from FIRE-3 and it had also recommended submission of data from CALGB 80405 in relation to RAS status when available. Consequent to the positive opinion from the CHMP on 26 June 2014, and with respect to FIRE-3 data, the SPC for cetuximab included the following (section 5.1);

Points of appeal

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study'

Merck Serono noted that the Panel had ruled a breach of Clause 7.2 since it was considered that the headline was not a fair reflection of the overall data in that it had not been placed within the context of the study's primary outcome. Merck Serono submitted that the context of the headline was very specific in that it stated very clearly RAS wild-type patients, and did not refer to the broader ITT population of KRAS wild-type patients in which the primary outcome had previously been reported. This was because the KRAS wild-type population was known to have patients with mutations beyond the KRAS EXON 2 mutations (which had been excluded following a protocol amendment in October 2008) and therefore contained a patient population predicted to be resistant to cetuximab. Consequently the primary endpoint on the basis of the intention-to treat (ITT) population would not be an accurate reflection of the clinical conclusions that could be drawn. It would be irrational to treat a patient with known RAS mutations with cetuximab; hence it was not rational to include such patients in an analysis of the potential clinical benefits of such a treatment, even though it might be statistically sound to do so. The RAS wild-type population referred to within the headline was therefore precise. The headline clearly stated that the analysis was 'New'; in other words not the first presentation of results.

Merck Serono submitted that clinicians who treated patients with metastatic colorectal cancer were well aware of the development of RAS testing and the implications of such testing in terms of efficacy of EGFR targeted therapies in defined patient populations. The headline provided new information which could help inform their clinical decisions. Further, the results of the comparison complained of was now incorporated into the licence for cetuximab that it was accurate and hence not misleading, and Merck Serono appealed the Panel's ruling of a breach of Clause 7.2.

2 First bullet point in press release; 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival from 25.6 months to 33.1 months (p=0.011)

Merck Serono noted that a breach of Clause 7.2 had been ruled since the Panel considered that it was not sufficiently clear at the outset that the analysis had been exploratory, and further that such analyses should not be used as the basis for a robust comparison of medicines, and hence the material had been insufficiently complete to enable the recipient to form their own opinion.

Merck Serono submitted that although statistically sound, the analysis of the primary endpoint in the ITT population could lead to clinically unsound conclusions in that the ITT patient population contained a subset of patient that would be resistant to treatment with cetuximab. Since the initiation of that study there had been a protocol amendment to exclude patients with KRAS mutation (of EXON 2). Consequently the ITT population was modified from that originally envisaged. Since that amendment new knowledge regarding the importance of RAS testing, expanded beyond KRAS EXON 2, had been made available, and as such the clinical comparison of the two medicines (cetuximab and bevacizumab) in the ITT population was no longer valid. The clinically meaningful comparison as presented within the press statement was between cetuximab in a non mutant RAS population and the comparator in the same patient population.

Merck Serono submitted that given the evolution of RAS testing and previous amendments to several trials in patients with metastatic colorectal cancer to exclude a KRAS mutant population, it argued that clinicians who treated patients with mCRC were well used to interpretation of analysis of patient subsets under these circumstances, and were able to determine the value of such analyses on their own. Merck Serono therefore appealed the Panel's rulings on this point, and reminded the Appeal Board that the information presented was accurate for the population defined, and this information was now incorporated into the licence for cetuximab.

Merck Serono submitted that Roche had also alleged a breach of Clause 7.4 stating that Merck Serono had not addressed sufficiently their [Roche's] concerns that the sub-group analysis needed to be accounted for statistically to avoid bias from multiple analyses. The Panel ruled that 'On balance and on this very narrow point' the bullet point was not capable of substantiation and hence ruled a breach of Clause 7.4.

Merck Serono submitted that such statistical analyses had indeed been undertaken, and had been scrutinised by the EMA, following which the results of the comparison complained with were now incorporated into the licence for cetuximab. The comparisons made within the bullet point were validated and therefore appealed the Panel's ruling on this point.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

Merck Serono submitted that in reaching its ruling on the above quotation the Panel had alluded to its previous comments with '... regard to the data from the FIRE-3 study showing a 7.5 month increase in median overall survival when using Erbitux plus FOLFIRI as compared with using bevacizumab plus FOLFIRI in metastatic colorectal', and consequently extrapolated these previous findings to the above quotation from Professor Heinmann.

The Panel stated that '... the quotation was misleading as within the context of the median survival data it applied disproportionate weight to the results thereby exaggerating Erbitux's properties and consequently did not encourage the product's rational use'. The Panel thus ruled breaches of Clauses 7.2, 7.10, and 10.2, and also noted its comments applied to Clause 22.2 and similarly ruled a breach of that clause.

Merck Serono submitted that it had argued that the information presented within the press statement was accurate, not misleading, capable of substantiation, and now integral within the licence for cetuximab and consequently it appealed the Panel's rulings.

Additionally Merck Serono submitted that it had argued for rational use of cetuximab based upon RAS status and had presented information on median survival specific to that patient population. This was for a smaller patient population than the licence allowed for at that time (KRAS EXON 2 wild-type), and represented the (smaller) patient population now reflected in the current licence. The update to the licence occurred in December 2013 and was based in part upon these data.

Merck Serono submitted that Professor Heinmann's quotation also continued 'Together with insights from other recent relevant studies, these results suggest that 1st line treatment of RAS wild-type patients should include an anti-EGFR therapy'. The press statement advocated rational prescribing in a specific patient population, rather than the contrary, and therefore Merck Serono appealed the Panel's ruling on this point and consequently appealed the Panel's rulings of a breach of Clause 22.2.

5 Overall

Merck Serono had noted the Panel's comments regarding breaches of Clause 9.1 and in particular Clause 2. The Panel had noted that '... it was very important that press releases about sensitive issues such as survival in cancer were fair, factual and not misleading,' and further that 'the press release had failed to reflect the study's primary endpoint'. Based upon the arguments expounded above Merck Serono submitted that the information regarding survival contained within the press statement was fair, factual and did not mislead. The survival data had subsequently been scrutinised by the EMA and included into the licence for cetuximab. This data was also clearly stated to relate to patients with RAS wild-type tumours, a subset from the FIRE-3 ITT population and therefore not applicable to the broader population in whom the primary analysis had been performed. It had also been stated within the press release that the primary endpoint of the study had not been achieved. Merck Serono rejected Roche's allegation of prejudicing patient safety, and again noted that the survival comparison complained of had been incorporated into the licence for cetuximab. Merck Serono submitted that its actions in releasing the press release at issue on 28 September 2013 did not reflect a lack of the high standards expected from the pharmaceutical industry, nor did it bring discredit to the industry; Merck Serono therefore appealed the Panel's ruling of breaches of Clauses 9.1 and 2.

RESPONSE FROM ROCHE

Before it commented on the specifics of Merck Serono's appeal, Roche stated that it wanted to be clear on its motivation for making this complaint. From the start, the objective was to gain commitment from Merck Serono to cease the use of unfounded claims of Erbitux superiority over Avastin in the first-line treatment of patients with RAS wild-type metastatic colorectal cancer (mCRC) on the basis of an exploratory analysis of a secondary endpoint within a sub-group of a sub-group of patients in the FIRE-3 clinical trial (i.e. the 'RAS wild-type' sub-group of the 'evaluable patient' sub-group). Furthermore, Roche had sought commitment from Merck Serono that it would not make overt claims on the sub-group analysis or include the data in any materials without fully contextualising the analysis in question.

Roche submitted that unfortunately, Merck Serono persistently refused to accept that it had breached the Code and this resulted in the matter being referred to the PMCPA. Importantly, Roche had never questioned the fact that clinicians were interested in comparisons between Avastin and Erbitux in RAS wild-type populations, however it asserted that this did not mean that less robust analysis could be presented as having greater validity simply because it was 'interesting'.

Roche stated that Merck Serono's appeal appeared to be based on an assertion that it was appropriate to use the FIRE-3 exploratory sub-group analysis in question in isolation and without full context for two principal reasons:

1 the Erbitux licence had since been restricted to the population included in the exploratory analysis.

2 the results of the exploratory analysis had apparently now been accepted by the EMA for inclusion into the Erbitux SPC – Merck Serono's implication appeared to be that the EMA review of the data and decision to allow it to be included in the SPC somehow gave it greater statistical validity than would normally be afforded to an exploratory sub-group analysis.

Roche alleged that these arguments were flawed and should make no difference to the rulings on the case for several reasons:

i) The PMCPA guidance on appeal procedures clearly stated that 'it must have been possible to substantiate a claim etc on the day it was made'. When the press release was issued the Erbitux licence matched the intention-to-treat (ITT) population of the FIRE-3 trial so was used the subsequent licence restriction was not relevant.
ii) The argument that the sub-group analysis would soon be in the SPC should hold no weight at all for rulings on materials issued in the past because when a company examined a press release to ensure it did not contravene

the Code, this was based on being able to substantiate the information at the time of examination/approval.

iii) Regardless of the above point, the notion that inclusion in the SPC made an exploratory sub-analysis more robust because it had been scrutinised by the EMA was simply not true. This did not alter Merck Serono's obligation to represent the data in a fair, balanced and contextualised manner.

iv) Independent guidance on the use of secondary endpoints and sub-group analyses (including guidance from the EMEA) supported point iii above by requiring caution with interpreting such data. Clearly when representing data which is based on both a secondary endpoint and in an exploratory sub-group in a trial which failed to meet its primary endpoint, the need for such caution would be even greater:

- EMEA Committee for Proprietary Medicinal Products (CPMP) advice: 'Points to consider on multiplicity issues in clinical trials' (2002):
  - Section 2.1.2 clarified that no confirmatory claims could be based on secondary endpoints in trials where the primary endpoint had not been met
  - Section 3.2 reiterated this point
  - Section 3.3: highlighted that further studies would be needed in this situation
- International Conference on Harmonisation (ICH) E9 guidelines: 'Statistical Principals for Clinical Trials' (1998):
  - Section 5.7 was clear on the need for caution when making treatment efficacy conclusions based solely on exploratory sub-group analyses
- Publication authored by Robert O'Neill of the Food and Drug Administration (FDA): 'Secondary endpoints cannot be validly analyzed if the primary endpoint does not demonstrate clear statistical significance' (1997):
  - Argued that caution was needed when making inferences for secondary endpoints when a trial has failed to meet its primary endpoint.

Licence updates:

Roche alleged that the update to the Erbitux licence to restrict its use to RAS wild-type patients (December 2013) only occurred after the press release was issued (September 2013) and so the FIRE-3 ITT population reflected the licensed population for Erbitux when the press release was issued and so was of very high clinical relevance.

KRAS and RAS proteins:

Roche alleged that this section of the Merck Serono appeal built the argument that reporting of outcomes by different RAS mutation status was important. This extensive section of the appeal missed the crux of the complaint and the Panel ruling which objected to the use of exploratory sub-group analysis to make unequivocal claims, and also the use of this analysis without full contextualisation.

Evolution of RAS testing:

Merck Serono commented that care should be exercised in drawing absolute clinical conclusions from primary endpoints in ITT populations which contained a subset of patients with RAS mutations making them resistant to Erbitux therapy. Roche alleged that this was presumably an attempt to justify why the ITT population primary endpoint results were not included in the press release. This argument was flawed for two reasons:

1 Roche alleged that the primary endpoint results in the ITT trial population were critical to set the context of the exploratory sub-group analysis both from a clinical and statistical perspective, especially when the exploratory analysis was not consistent with the outcome of the overall trial which failed to meet its primary endpoint for demonstrating superiority of Erbitux over Avastin in overall response rate (ORR).
2 Roche alleged that as already stated, the ITT population for FIRE-3 reflected the licensed indication for Erbitux at the time of the press release. Roche questioned the relevance of the OPUS and CRYSTAL post-hoc analyses to this appeal. RAS analysis for the CRYSTAL and OPUS trials were not reported at the time the press release was issued, meaning that the data provided in Merck Serono's appeal on OPUS and CRYSTAL was irrelevant as it was retrospective justification. Furthermore, these analyses compared Erbitux plus chemotherapy with chemotherapy alone so did not specifically address the question of whether Erbitux plus chemotherapy was superior to Avastin plus chemotherapy in the first-line treatment of mCRC.

Roche alleged that importantly, the point made by Merck Serono that dismissing such exploratory analysis on the basis of purely statistical grounds would not be appropriate clinically and could affect patient care missed the point of the core complaint and the Panel ruling: the requirement to not make overt claims on the basis of the analysis and to fully contextualise it did not constitute dismissing such exploratory analyses. The use of unsubstantiable and misleading claims and the omission of full contextualisation which could have a negative impact on patient care.

Analysis of FIRE-3

Roche alleged that Merck Serono's detailed summary of FIRE-3 only further supported its arguments of the importance of providing full context whenever the trial results were discussed. Roche asked the Appeal Board to contrast the full results of the trial and the complex discussion in Merck Serono's appeal with the selective claims and relative prominence given to data included in the press release as Roche believed this spoke for itself.

Roche noted that Merck Serono proceeded to discuss the results of FIRE-3 in its appeal and unequivocally state the OS difference of 7.5 months in the RAS exploratory sub-group analysis that this was not a chance finding. How would Merck Serono know this in view of the EMEA and FDA guidance mentioned

earlier which highlighted the potential for 'false positive' results in such analyses? The guidance from these independent bodies asserted that further prospective trials should be undertaken to validate such findings. In fact, the interim primary endpoint results from the CALGB 80405 trial (mentioned by Merck Serono) showed no difference between the two arms, reinforcing the possibility that the OS difference seen in the KRAS wild-type population of FIRE-3 might have been a false positive result. This clearly added further questions as to the validity of further sub-analyses of this secondary endpoint in FIRE-3.

Roche alleged that experience was that the results of FIRE-3 had caused significant confusion in the clinical community precisely because they were not consistent with the existing evidence base and (by Merck Serono's own admission) raised some key questions specifically on the validity of the OS sub-group analysis for RAS wild-type patients. The questions of how an OS advantage could be demonstrated in the absence of any difference in PFS, and why the Kaplan-Meier curves only started to separate long after cessation of first-line treatment were ones for which there were no conclusive scientific explanations. The reality was that there were three possibilities:

1 The OS results from FIRE-3 study sub-group analysis were chance findings
2 The OS results were not a chance finding but were the result of something other than the first-line treatment
3 The OS results were due to a real effect of first-line Erbitux.

Roche alleged that crucially, there was no way of knowing which of the above was true without a well-planned, prospective randomised, controlled trial (RCT) in RAS wild-type patients as part of a confirmatory strategy. It was important for patients that treatment decisions were not based on reverse-analysis of studies in isolation, but instead were appropriately informed by prospective RCTs, with less robust analysis represented accurately and objectively in clear context.

Roche alleged that Merck Serono had attempted to further justify its belief that Erbitux was driving the OS difference seen in FIRE-3 by introducing the PEAK study at this point as supporting evidence. It was important to note that the phase II PEAK trial did not investigate Erbitux but a different EGFR inhibitor. Within the publication itself it was explicitly stated that it did not plan to test any formal hypotheses and therefore it was conducted to look for trends and for opportunities to potentially launch a subsequent, prospective phase III trial. As such, it did not provide evidence that the OS results in FIRE-3 were due to a real effect of Erbitux as implied by Merck Serono.

Roche alleged that overall, regardless of the nuances within the data, what was clear from both Merck Serono's appeal and Roche response was that this was currently an area with no clear answers and as such, Merck Serono's simplistic and unbalanced representation of the data, and unequivocal claims of superiority in its press release was clearly at odds with this and could seriously mislead the audiences.

Points of appeal

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'

As commented earlier, Roche alleged that these were numerous reasons why it considered that Merck Serono's grounds for appeal were flawed:

- Much of Merck Serono's appeal was irrelevant as it was based on retrospective information/ data
- The fact that the ITT results had been reported previously did not justify omitting them in the press release because all items needed to comply with the Code in their own right
- The headline claim was based on an exploratory sub-group analysis which by definition was hypothesis-generating – not a sound basis for making an overt claim of superiority – the context for this was insufficiently prominent or lacking altogether
- Merck Serono argued in its appeal that 'it would be irrational to treat a patient with known RAS mutations with cetuximab (Erbitux)' yet this important patient safety-related point was omitted from the press release which focussed on the argument for why RAS wild-type patients should receive Erbitux
- Merck Serono's justification that 'clinicians who treated patients with mCRC were well aware of the development of RAS testing and the implications of such testing in terms of efficacy of EGFR targeted therapies in defined patient populations' was flawed on two levels:
  - Even if true this would not negate the requirement of the Code to provide fair and balanced information
  - Merck Serono had confirmed that the press release was issued to 40 medical and pharmaceutical titles, 23 health journalists at national print and online titles and 16 freelance health journalists. Clearly not all of these recipients could be expected to have the necessary depth of understanding of the mCRC treatment environment. This point seemed to suggest confusion within Merck Serono as to the audience and intention of the press release.

2 First bullet point in press release: 'New data from the pre-planned analysis of the FIRE-3 study show an increase of median overall survival from 25.6 months to 33.1 months (p=0.011)'

Roche alleged that Merck Serono's appeal appeared to argue that its representation of the data was acceptable because the RAS analysis was a more 'clinically meaningful' comparison. However interesting or clinically relevant an exploratory analysis was (pre-planned or otherwise) it did not change the fact that the analysis was exactly that - an exploratory analysis. By definition, such analyses should be used to generate hypotheses

which might be validated as primary endpoints in ITT populations through appropriately powered, prospective, randomised clinical trials - the results of which might then validate whether the exploratory analysis was simply a chance finding or not. None of the arguments presented by Merck Serono made a material difference to the Panels ruling.

Roche alleged that furthermore, it was a post-authorisation safety requirement by the EMA that Merck Serono was obligated to submit the results of the FIRE-3 RAS analysis, and this would be incorporated into the Erbitux SPC over 9 months after the issue of the press release. Therefore this did not mean that this superiority claim in the press should be considered capable of substantiation at the time of issue. Aside from this, the important point still remained that inclusion in the Erbitux SPC still would not justify, validate or substantiate an overt claim of Erbitux superiority over Avastin based on an exploratory sub-group analysis.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

Roche alleged that again, the imminent inclusion of the FIRE-3 RAS analysis into the Erbitux SPC was retrospective and therefore not relevant. Furthermore even following SPC inclusion, this quotation continued to be misleading as it still applied disproportionate weight to the exploratory sub-group analysis results and thereby exaggerated Erbitux's properties, thus not encouraging its rational use.

Roche alleged that in addition, NHS England Cancer Drugs Fund data provided evidence that the above quotation did not represent the views of the majority of the clinical community in England since the relative proportions of applications by clinicians for patients to access Avastin and Erbitux for the first-line treatment of mCRC did not indicate a significant change since the FIRE-3 results were presented. This view was also supported by the National Comprehensive Cancer Network (NCCN) Guidelines on Colon Cancer (Version 3.2014) which were critical of the FIRE-3 trial and indicated the need to await further data from other studies to conclude whether these were differences in efficacy between Avastin and Erbitux in relevant patient populations.

5 Overall

Roche alleged that Merck Serono's appeal against the Panel's ruling of breaches of Clauses 2 and 9.1 again centred around its overarching points commented on above earlier. Again, Roche felt strongly that these arguments were both retrospective and irrelevant in that an exploratory sub-group analysis still needed to be clearly and overtly placed into appropriate context, regardless of whether it was included in an SPC or not. None of Merck Serono's arguments justified the use of a hypothesis-generating exploratory sub-group analysis to make unbalanced, uncontextualised and misleading claims around a sensitive issue such as survival in cancer.

Roche noted that Merck Serono had not appealed Point 3 above, thus accepting that it had breached the Code in this regard. This misrepresentation of the data (by implying equivalent efficacy with Avastin in a population within the Avastin licence but outside of the Erbitux licence, based on a retrospective pooled analysis of two different populations of RAS mutations from two different time points) could have potentially serious consequences for patient safety.

Furthermore, Roche noted through its appeal that Merck Serono repeatedly asserted that KRAS wild-type patient populations included a sub-group or patients with RAS mutations who were highly unlikely to respond to Erbitux. Merck Serono used this point to build an argument that this somehow justified its decision to not include full, overt context of the exploratory sub-group analysis in its press release. Roche was confused by this argument as it seemed to raise an important question: if Merck Serono was aware of this at the time of the press release (and would like this to be taken into account in the appeal) then why did it focus exclusively on claims of superiority over Avastin in the material, and omit any mention of this important point relating to patient safety in the press release – instead stating in the press release that 'no new safety signals were observed'?

Additionally, Roche stated that it had raised concerns with Merck Serono and the PMCPA that claims similar to those ruled in breach in this case were being used by Merck Serono in promotional materials. Merck Serono stated that the claims were always set in context and since Roche was not able to provide evidence to the contrary the Panel was unable to rule on this. Roche was now in possession of promotional materials (example provided) which made overt promotional claims on the FIRE-3 exploratory sub-group analysis without, as Merck Serono had indicated, providing full and appropriate context. This suggested a concerning misrepresentation of the data across multiple communication channels. (This material was not subject of the appeal; both parties were so advised.)

Overall, Roche considered that the Panel's ruling of breaches of Clauses 9.1 and 2 were entirely justified as Merck Serono's appeal arguments were predominantly retrospective and even if taken into consideration, they still did not justify the overt claims and lack of full, clear and prominent contextualisation of exploratory sub-group analysis which formed the basis of the breaches of the Code in this case.

APPEAL BOARD RULING

The Appeal Board noted that this was clearly a complex area. As the FIRE-3 study had progressed it had started to become clear that patients with RAS wild-type mCRC responded better to therapy than those with RAS mutations. The analysis at issue in the press release involved only the RAS wild-type patients (n=342) and not the original ITT population (n=592). Although the Erbitux marketing authorisation had been restricted to patients with

RAS wild-type mCRC, this was not the case when the press release was issued on 28 September 2013. In that regard the Appeal Board considered that only the data that was available on that date could be relied upon to substantiate the content of the press release.

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'

In the Appeal Board's view, it was not clear that the new analysis referred to in the bold, prominent heading was an exploratory, retrospective, sub-group analysis of the secondary endpoint of the study. There was a strong possibility that the heading would be incorrectly assumed to refer to the primary endpoint. It was not clear from the outset that the FIRE-3 study had failed to meet its primary endpoint; this was only stated in the third paragraph on page 2.

The Appeal Board noted that when the press release was issued, Merck Serono had one finding in a retrospective analysis of a secondary endpoint that suggested a possible interesting effect in a sub-group of mCRC patients. The Appeal Board doubted whether the study was powered to show whether or not this finding was due to chance and thus a further study would be required to confirm the results. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the presented secondary endpoint findings. The Appeal Board considered that the heading was misleading as alleged and it upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

2 First bullet point in press release: 'New data from the pre-planned analysis of the FIRE-3 study show an increase of median overall survival from 25.6 months to 33.1 months (p=0.011)'

The Appeal Board considered that its comments above at Point 1 were relevant here. The Appeal Board noted that the exploratory nature of the analysis was not stated. The sub-group analyses had not been placed in the context of the study's failure to achieve its primary endpoint. The Appeal Board considered that 'New data from a pre-planned analysis...' implied that this was the ITT population when it was not. The Appeal Board noted that Merck Serono's representatives at the appeal had described the new data as both a retrospective finding and a pre-planned analysis which was confusing. The Appeal Board could see no evidence that the analysis was pre-planned. The Appeal Board considered that the bullet point was misleading as alleged; not enough information had been presented to enable readers to form their own opinion of the therapeutic value of Erbitux. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board considered that although it had concerns as to whether the analysis was sufficiently powered, the bullet point was nonetheless factually correct and thus on balance, on this very narrow point, was capable of substantiation. No breach of Clause 7.4 was ruled. The appeal on this point was successful.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

The Appeal Board noted the full statement referenced to the FIRE-3 principal investigator, on page 2 of the press release stated 'These new data from the Phase III study FIRE-3 show a 7.5-month increase in median overall survival to 33.1 months when using 1st line Erbitux plus FOLFIRI as compared to using bevacizumab plus FOLFIRI in metastatic colorectal cancer. Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'. The Appeal Board considered that the FIRE-3 principal investigator had referred to the increase in the time of median overall survival as the 'paradigm shift'. However, this claim did not refer to the fact that the patient population at issue was restricted to those with wild-type RAS. In the Appeal Board's view the claim appeared to apply to all mCRC patients and that was not so. The Appeal Board was also concerned that the claim strongly implied that the findings were clinically meaningful yet in effect, when the press release was issued, they were no more than suggestive of a potential effect.

The Appeal Board noted its comments and rulings above and considered that the quotation was misleading as it gave undue weight to the median overall survival data given that it came from an exploratory, sub-group analysis. The Appeal Board noted that by contrast, a presentation given by Professor Heinmann had referred to the overall survival data in the context of the failed primary endpoint in the ITT group. The Appeal Board considered that the quotation, within the context of the press release, exaggerated Erbitux's properties and implied that the results were true for all mCRC patients and as such did not encourage the rational use of the product. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.10 and 10.2. The appeal on this point was unsuccessful.

The Appeal Board further considered that if the press release was found on the Internet by mCRC patients (or their carers), it might give them, particularly those without RAS wild-type mCRC, unfounded hopes about their potential treatment and it thus upheld the Panel's ruling of a breach of Clause 22.2. The appeal on this point was unsuccessful.

5 Overall

The Appeal Board noted its rulings of breaches of the Code above. It also noted the Panel's rulings of breaches in Point 3 which were not appealed. It considered that Merck Serono had failed to maintain high standards. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board noted that both it and the Panel (Point 3 above) had considered that the press release did not encourage the rational use of Erbitux. The Appeal Board also considered that the failure of the press release to refer to relevant contra-indications (also noted by the Panel at Point 3 above) raised concerns with regard to patient safety. In the Appeal Board's view, it was extremely important for patients, and the NHS, that press releases about sensitive issues such as survival in cancer were not misleading. Overall, the Appeal Board noted its comments above and the nature of the breaches of the Code ruled and decided to uphold the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **17 March 2014**

Case completed **10 October 2014**

Case AUTH/2714/5/14

CONSULTANT RHEUMATOLOGIST v PFIZER

Conduct of a representative

A consultant rheumatologist, complained about the conduct of a Pfizer medical representative and that of his/her manager.

The complainant explained that he/she had agreed to a 'ten minute catch up' with the representative and on the day the line manager accompanied the representative. The representative started by enquiring about the complainant's health as the previous year the complainant had been unwell. The complainant submitted that he/she found this extremely uncomfortable and inappropriate as he/she did not really know the representative and believed they had only met briefly once before. The complainant considered that his/her health problems were a private issue and did not appreciate the representative discussing them, particularly in front of his/her line manager who the complainant had not spoken to before. In the complainant's view this was clearly a misguided attempt to appear 'pally'.

The complainant submitted that the representative then discussed Enbrel (etanercept) in psoriatic arthritis and ankylosing spondylitis. The complainant explained that he/she did not currently prescribe biologics for these conditions because of work done with regional specialists. The representative then asked what the complainant would use first line in these conditions; the complainant would normally use a monoclonal antibody, not Enbrel. The representative asked why, and the complainant replied because there was better data available for it with regard to extra-articular manifestations. The representative then asked the complainant why and what information that was based upon. The complainant reminded the representative that he/she did not have to justify prescribing decisions to him/her; this might be discussed with peers but not the representative. At this point the representative 'backed off' the questioning but shortly afterwards pressed the complainant again about prescribing habits and why he/she would prescribe a monoclonal antibody first. The complainant told the representative to stop pressing him/her about this and reiterated this was not his/her role. The complainant considered that the representative was trying to put on a show for his/her manager who had not said anything to the representative although it was clear that the complainant had got quite angry on two occasions.

Despite this, the representative asked why the complainant would use a monoclonal antibody as they had a longer half-life and then asked if the complainant knew that he/she had had a patient in the intensive therapy unit (ITU) over Christmas who had taken golimumab (Simponi co-marketed by Merck Sharp & Dohme and Janssen). The complainant explained that firstly, this was none of the representative's business; as the representative was not a clinician he/she should not discuss individual patients with anyone. It was completely inappropriate for the representative to try and discuss this with the complainant as the representative would not know the full story and whether golimumab was involved. The complainant stated that he/she would not expect any of the representatives from Merck Sharp & Dohme or Janssen to discuss any potential complication on Enbrel. At this point the complainant ended the meeting.

The complainant was extremely angry about the meeting and so called the representative's line manager. The complainant expected the manager to state that the representative had overstepped the mark, behaved inappropriately and apologise. If he/she had done that then the complainant would probably have accepted the apology. However the manager's reply was that when the representative realised that maybe he/she had gone too far' he/she 'backed off'. The complainant explained to the manager that this was not so; although the representative backed off initially he/she returned to the same line of questioning. The complainant considered that the manager was defending the representative's actions and certainly did not apologise for them. The manager did apologise if the complainant considered that the representative had gone too far but not that the representative acted inappropriately. That was very different from apologising for the representative's actions.

The complainant previously had good relationships with Pfizer and was therefore quite shocked as he/she had never been spoken to by any representative like that. The complainant had written to Pfizer but considered its response inadequate. The complainant had not had an apology from the representative or his/her manager.

The detailed response from Pfizer is given below.

The Panel invited further comments from the complainant and subsequently further information from Pfizer. Details were given below.

The Panel noted that there were differences in the parties' accounts of what happened it was extremely difficult in such cases to know exactly what had transpired. The complainant bore the burden of proof on the balance of probabilities. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually required before an individual was moved to complain.

The Panel noted that the complainant felt extremely uncomfortable when the representative enquired about his/her health problem as it was a private issue and the complainant could not recall ever

meeting the representative before or mentioning any illness to him/her. The Panel noted Pfizer's submission that the complainant had previously mentioned his/her illness to the representative and therefore he/she considered it appropriate and courteous to ask about it before talking about Enbrel and in the representative and his/her manager's view the complainant engaged in the discussion and did not appear to be uncomfortable. The Panel did not know what had been said by each party regarding the complainant's health issue. The Panel considered that whilst a general enquiry from a representative about a personal health issue might be appropriate and courteous, for a representative to initiate a detailed conversation about a personal medical matter might not be so and particularly when others were present.

Pfizer submitted that with regard to the patient on ITU, the representative stated that the case was previously disclosed by the complainant when they met in April 2013 and at no point did the representative have any personal information about the patient. The complainant disagreed that he/she had ever discussed any patient with an infection on monoclonal antibody with the representative and had no recollection of the April 2013 meeting. The Panel noted that the interaction between the repesentative and the complainant in April 2013 was, according to Pfizer's call records, at a group meeting that both had attended rather than a one to one call.

The Panel noted Pfizer's submission that whilst the representative recognized that on two occasions the complainant was irritated by his/her approach, he/she quickly broadened the discussion or changed the subject in an attempt to de-escalate the situation. The complainant, however, submitted that in his/her view there was no indication that the representative recognised that he/she was irritated during the consultation and queried why he/she felt the need to return to the discussion about extra-articular manifestations of psoriatic disease if he/she was aware of the complainant becoming irritated on the first occasion.

The Panel noted the complainant's allegation that the representative had questioned his clinical judgment. The Panel noted Pfizer's submission that in the course of a meeting between a company representative and a health professional it would not be unusual to discuss a clinician's prescribing strategy or appropriately challenge a clinician's prescribing strategy with fair and balanced information to suggest reasonable alternative prescribing decisions.

The Panel noted that the complainant stated that he/she had not discussed any patient with an infection on a monoclonal antibody. The only one patient he/she had ever had on golimumab remained well and the complainant stated that he/she had had no one admitted to ITU on any biological therapy since he/she had started working at the hospital. The Panel noted that according to Pfizer the complainant and representative had attended a meeting in April where the discussion about the patient in ITU took place. Pfizer had not commented further on the complainant's statements in this regard. The Panel considered that the health professional would know what had happened to his/her patients.

The Panel noted that it was unfortunate that the complainant was upset by the interaction, nonetheless, it considered that there was no evidence before it to indicate on the balance of probabilities that the two elements of the discussion referred to by the representative were such as to disparage the complainant. It was impossible to determine where the truth lay. The Panel thus ruled no breach of the Code. This ruling was appealed by the complainant.

The Panel noted the differences between the accounts which involved one person's word against another. It also noted the cumulative effect of the matters raised by the complainant. The Panel considered however that there was not sufficient evidence to show that on the balance of probabilities that either the representative or the company had failed to maintain high standards; no breaches of the Code were ruled including Clause 2. These rulings were appealed by the complainant.

The Appeal Board considered that, upon appeal, the complainant had provided evidence to show that the patient in ITU on golimumab did not in fact exist. The Appeal Board noted from the complainant that this was the focus of the appeal as the complainant disputed, on a point of principle, the representative's submission that he/she had ever discussed any of his/her patients with any medical representative. The complainant could find no records to correlate with Pfizer's CRM entries for meetings with the representative. The complainant could not recall previously meeting the representative or his/her manager before the meeting at issue in January 2014. The complainant acknowledged that he/she might have seen them at some point but could not recall a meeting. Any meeting would have been limited to a greeting. The complainant also stated that the nature of his/her previous illness was known and the representative might have easily found out about it from other staff.

The Appeal Board was extremely concerned that Pfizer had not re-interviewed the representative or the manager in light of the new evidence provided in the appeal. This was despite the fact that the company agreed that the new evidence suggested that the ITU patient did not exist and that the prior meeting might have been misremembered or not happened. The Appeal Board was concerned that Pfizer had not questioned its representative or line manager to establish whether he/she had mistaken the complainant for a different doctor in a different hospital or had, in fact, fabricated the previous interaction. Either way the Appeal Board considered that on the balance of probabilities, it was satisfied that the representative had not discussed a patient in ITU on golimumab with the complainant in April 2013.

The Appeal Board noted that the representative's CRM entry for the meeting in April 2013, at which he/she stated he/she had discussed the patient in ITU with the complainant, did not include any notes about the meeting. Only one of the five CRM

entries had a note. The complainant disputed the representative's submission. The Appeal Board considered that Pfizer should have explored the lack of CRM notes. The Appeal Board was concerned that the meeting at which the representative claimed to have first discussed a patient in ITU on golimumab with the complainant was nine months before the meeting at issue in January 2014 and yet, without any call notes to refer back to, the representative had managed to recall detailed information about that discussion.

The Appeal Board noted that Pfizer recognized that there were significant discrepancies between the complainant's account of the meeting in January and that of the representative and manager.

The Appeal Board noted the complainant's submission that he/she never discussed his patients with medical representatives. The Appeal Board considered that, given the evidence before it, on the balance of probabilities, in April 2013 the representative could not have discussed with the complainant one of his patients who was on golimumab and admitted to ITU as such a patient did not exist within the complainant's hospital either then or since; the reference to such a discussion at the meeting in January 2014 was thus unacceptable. The Appeal Board considered therefore that the representative had failed to maintain a high standard of ethical conduct; a breach of the Code was ruled. The appeal on this point was successful. Noting this ruling and its comments above the Appeal Board also considered that Pfizer failed to maintain high standards and it ruled a breach of the Code. The appeal on this point was successful.

The Appeal Board noted at the appeal that the complainant indicated that the appeal did not relate to the alleged disparagement. The Appeal Board thus upheld the Panel's ruling of no breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board did not consider that the circumstances of this case warranted a ruling of a breach of Clause 2 and it upheld the Panel's ruling in that regard. The appeal on this point was unsuccessful.

A consultant rheumatologist, complained about the conduct of a Pfizer medical representative, and his/her manager.

COMPLAINT

The complainant explained that he/she had agreed to a 'ten minute catch up' with the representative in question. On the day, the representative had turned up with his/her line manager although he/she had not previously indicated that the manager would be there. The representative started by enquiring about a serious health problem that the complainant had had the previous year which required surgery and some time off work. The complainant submitted that this was extremely uncomfortable and inappropriate as he/she did not really know the representative and believed he/she had only met him/her briefly once before. The complainant considered that his/her health problems were a private issue and he/she did not appreciate the representative's discussing them, particularly in front of his/her line manager who the complainant had not spoken to before. The complainant considered that this was clearly a misguided attempt to appear 'pally' with him/her, but he/she did not appreciate it at all.

The complainant submitted that the representative then discussed Enbrel (etanercept) and its use in psoriatic arthritis and ankylosing spondylitis. The complainant explained that he/she did not currently prescribe biologics for these conditions because of work done with regional specialists. The representative then asked what the complainant would use first line in these conditions and the complainant stated that he/she would normally use a monoclonal antibody, not Enbrel. The representative asked why, and the complainant replied that there was better data available for it with regard to extra-articular manifestations. The representative then asked why the complainant considered that and what information that was based upon. The complainant submitted that at this point he/she reminded the representative that he/she did not have to justify his/her prescribing decisions to him/her; he/she might discuss this sort of thing with peers but not him/her. At this point the representative 'backed off' the questioning but shortly afterwards started pressing the complainant again about his/her prescribing habits and why he/she would prescribe a monoclonal antibody first. The complainant told the representative to stop pressing about this and reiterated that it was not his/her role to quiz him/her on this. The complainant strongly considered the representative was trying to put on a show for his/her manager who had not said anything to the representative although it was clear that the complainant had got quite angry on two occasions.

Despite this, the representative asked why the complainant would use a monoclonal antibody as they had a longer half-life. The representative then asked if the complainant knew that he/she had had a patient in the intensive therapy unit (ITU) over Christmas who had taken golimumab (Simponi co-marketed by Merck Sharp & Dohme and Janssen). The complainant explained that firstly, this was frankly none of the representative's business; as the representative was not a clinician he/she should not discuss individual patients with anyone. It was completely inappropriate for the representative to try and discuss this with the complainant as the representative would not know the full story and whether golimumab was involved. The complainant stated that he/she would not expect any of the representatives from Merck Sharp & Dohme or Janssen to discuss any potential complication on Enbrel. At this point the complainant told the representative to stop talking as it was not his/her business and shortly afterwards said goodbye.

The complainant submitted that he/she was left feeling quite upset and extremely angry about the meeting and so called the representative's line manager to ask how he/she considered the representative had behaved. The complainant expected the manager to state that the representative had overstepped the mark, behaved inappropriately and apologise. If he/she had done that then the

complainant stated that he/she probably would have accepted the apology. However the manager's reply was that when 'the represenative realised that maybe he/she had gone too far' he/she 'backed off'. The complainant explained to the manager that he/she did not consider that was so; although the representative backed off initially he/she returned to the same line of questioning. Without saying much the complainant considered that the manager was defending the representative's actions and certainly did not apologise for them. The manager did apologise if the complainant considered that the representative had gone too far but stated that he/she did not consider that the representative acted inappropriately. That was very different from apologising for his/her actions.

The complainant submitted that he/she had previously had very good relationships with the Pfizer team and was therefore quite shocked to have been treated like this; he/she had never in his/her medical career been spoken to by any representative like that. The complainant had written to Pfizer but considered its response (copy provided) inadequate. The complainant had not had an apology from the representative or his/her manager.
When writing to Pfizer, the Authority asked it to consider the requirements of Clauses 2, 8.2, 9.1 and 15.2 of the Code.

RESPONSE

Pfizer acknowledged that the representative in question and his/her manager visited the complainant for a planned call in January 2014. The meeting lasted approximately 20-30 minutes and started with the representative introducing his/her manager and asking the complainant if he/she had any objections to the manager being there. The complainant did not raise any objections to the manager's presence.

The representative first asked how the complainant was as he/she had previously mentioned his/her illness to the representative and therefore he/she considered it appropriate and courteous to start by asking how the complainant was before talking about Enbrel. Pfizer submitted that the complainant engaged in this discussion and spoke about his/her recovery and a subsequent return to work. The complainant commented that he/she had not seen either the representative or the other local representative for several months. In response, the representative stated that they had not wanted to disturb the complainant when he/she had just returned to work. During this opening conversation the complainant stated that he/she had recently taken on a role at a university and that this occupied a fair amount of time. Overall this opening lasted about 5-10 minutes. Pfizer submitted that the complainant appeared to engage in the conversation and did not appear to be uncomfortable.

The next 5-10 minutes of the meeting were spent discussing Enbrel in relation to psoriatic arthritis. The complainant stated that his/her opportunities to prescribe in psoriatic arthritis were limited as it was departmental policy to refer patients who required a biologic in psoriatic arthritis to another consultant. Pfizer stated that the representative asked the complainant, if he/she was able to prescribe biologics in psoriatic arthritis in the future, what he/she would use. The complainant said he/she would not use Enbrel because of the risk of uveitis and that he/she would use a monoclonal antibody, probably adalimumab. This was a common point of discussion within this disease area and would be an appropriate topic for a specialist representative to discuss with a consultant. The representative discussed the incidence of uveitis with the complainant and highlighted that other local experts in the field had suggested that the risk of developing uveitis would not affect their prescribing decisions. The complainant stated that that was up to them and whilst he/she agreed it was a relatively low incidence it was real enough for him/her to prefer to use a monoclonal antibody before Enbrel. The complainant stated that he/she had reviewed all the clinical data and had been involved in a clinical review about it and that was his/her conclusion. During this part of the call the complainant appeared to speak with a raised voice. The representative asked if the complainant would like a colleague from the medical department to speak to him/her about Enbrel and uveitis but he/she declined on the basis that he/she had reviewed the literature.

As the representative recognised that the complainant was irritated with the conversation, he/she broadened it to discuss the overall efficacy and safety profile of Enbrel. The representative did return to the topic of uveitis and asked whether the benefits of Enbrel that he/she had described might outweigh the relatively low incidence of uveitis? The complainant stated that he/she did not like the discussion and said in his/her view, the representative had questioned his/her clinical judgment. The representative tried to clarify that he/she was just trying to convey the clinical benefits of Enbrel and understand the complainant's position. The representative absolutely did not question the complainant's clinical judgment in any way.

The representative mentioned a patient case history that the complainant had spoken to him/her about in April 2013. The representative had no personal information about the patient and had not heard about the patient from any source other than the complainant. The complainant had mentioned during the previous call in April that the patient had been on ITU and had received a monoclonal antibody, ie golimumab. The patient had problems with infection and had been complicated to manage, although cause and effect could not be confirmed. In response to this example the complainant noted that this was of course just one patient and not a clinical trial and therefore conclusions should not be drawn from it. The complainant confirmed that he/she used Enbrel in patients with rheumatoid arthritis but would not use it in patients with psoriatic arthritis or ankylosing spondylitis. The representative stated that he/she was sorry if the complainant had been irritated by the discussion and he/she changed the topic completely to discuss medical education.

The final 5-10 minutes of the meeting were spent discussing an educational programme and also an upcoming company-sponsored educational meeting.

The complainant was very complimentary about the educational content of both meetings. Both the representative and his/her manager thought that the meeting concluded amicably.

Pfizer submitted that discussion of a personal medical matter was neither the purpose nor objective of the call. Similarly the company did not endorse nor support the recording of such information by company employees either in customer relationship management databases (CRMs) or informally. The representative's inquiry of how the complainant was following his/her return to work was intended only to be a genuine pleasant exchange before the start of the formal part of the call. The complainant had discussed his illness with the representative before and therefore it was courteous to ask how he/she was. The complainant engaged in this discussion about his/her return to work and actively shared and participated in this conversation (which lasted 5-10 minutes) and did not demonstrate any discomfort in discussing it at the time.

Pfizer provided a print out from the customer relationship management (CRM) database for review. A briefing document clearly described what should and what should not be entered by representatives in the CRM system.

Pfizer stated that no promotional materials were used in this meeting. The complainant requested a clinical paper and this request was forwarded to medical information.

With regard to the patient on ITU, the representative stated that the case was previously disclosed by the complainant when they met in April 2013. During this meeting the complainant had mentioned that the patient had experienced problems with infection and had been complicated to manage. At no point did the representative have any personal information about the patient. The representative did not hear about the patient from any source other than the complainant at their previous meeting.

The representative recognized that the complainant became irritated on two occasions. On the first occasion the representative was sensitive to this and broadened the discussion to talk about the overall efficacy and safety profile of Enbrel and then put the relatively low incidence of uveitis in the context of the overall benefits. On the second occasion the representative was again sensitive to this and changed the topic completely to discuss educational meetings.

Pfizer stated that in the course of a meeting between a company representative and a health professional it would not be unusual to discuss a clinician's prescribing strategy. Similarly it would not be unusual to appropriately challenge a clinician's prescribing strategy with fair and balanced information that would suggest alternative prescribing decisions were plausible. In this case, the representative highlighted that the development of uveitis was uncommon and went on to place this in the context of the overall efficacy and safety profile of Enbrel.

The representative's manager did not intervene in the call because the representative broadened the discussion the first time the complainant became irritated and then changed the topic completely on the second time. The representative apologized to the complainant and made it clear that he/she would move the discussion away from Enbrel and talked about Pfizer's educational meeting programmes. The complainant was complimentary about these educational meetings and the representative and his/her manager thought that the call ended amicably.

Pfizer provided a copy of the screen shots from its CRM that documented the call. As the complainant contacted the representative's manager after the call to make a complaint, the representative was asked to write up the call notes for an internal investigation rather than enter them in the CRM as per a routine call. This was why the notes were not in the CRM system. The complaint was escalated in mid January to the representative's manager's manager and then to a senior director. The complainant was contacted by a senior director three day's later.

Pfizer confirmed that both colleagues had passed their ABPI representative exam.

While Pfizer recognized that the meeting between the complainant the representative and his/her manager was a difficult interaction, it did not consider that this case represented a breach of Clauses 8.2, 15.2, 9.1 or Clause 2 of the Code.

Pfizer stated that with respect to Clause 8.2, the complainant's scientific or clinical opinion was never disparaged. The representative clearly recognized that on the two occasions the complainant was irritated by his/her approach, he/she quickly broadened the discussion or changed the subject in an attempt to de-escalate the situation. At no point did the representative claim or state that the complainant was incorrect or that his/her clinical or scientific opinions were unfounded. The representative merely provided an alternative interpretation of the relative importance of uveitis in the clinical decision making process based on the overall efficacy and safety profile of Enbrel and the interpretations of other experts in the field. As such Pfizer denied a breach of Clause 8.2.

With regard to Clause 15.2, although the representative referred to a previous conversation about a patient on ITU that had suffered an infection and was complicated to manage while receiving an alternative medication, Pfizer did not believe that this was evidence of a breach of this clause. At no point did the representative have any personal information about the patient. The representative did not hear about the patient from any source other than the complainant at their previous meeting.

With respect to a concern that the representative was over familiar with the complainant in the preliminary part of the call, Pfizer noted that the representative had only referred to the complainant's previous illness in the context of inquiring about his/her well being. The complainant had discussed this previously with the representative and it was

therefore considered appropriate and courteous to ask how he/she was. At no point during this preliminary part of the call did the complainant express a wish to change the subject and he/she actively engaged in the discussion. Pfizer recognized that there was a line between over familiarity and professional courtesy, however, it did not believe that the representative's actions represented a breach of the high standard of ethical conduct in the discharge of his/her duties, and as such it denied a breach of Clause 15.2. Furthermore the representative had met the complainant several times before so Pfizer considered that a certain level of familiarity was acceptable.

With regard to Clauses 9.1 and 2, Pfizer noted that it provided relevant briefings and guidance to its representatives on the appropriate conduct expected of them. Additionally, Pfizer had ensured that its representatives had been briefed on the appropriateness of content to be recorded in its CRM system. Similarly, Pfizer made it a priority to ensure that its representatives were trained appropriately on the materials that they used and it confirmed that both the representative and his/her manager were up-to-date with their training. Pfizer took the complaint very seriously and it launched an internal investigation into the conduct of the representative and his/her manager as soon as it received the complainant's letter. The investigation did not find any evidence of serious misconduct or breaches of the Code. As such Pfizer did not consider that it had failed in its responsibilities to maintain high standards and, as such, had not brought discredit to, or reduced confidence in the pharmaceutical industry.

Pfizer apologized for the anxiety and distress caused to the complainant and that had been expressed to him/her both verbally and in writing by senior Pfizer staff throughout the time from the initial complaint in January through to Pfizer's recent letter to the complainant.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant submitted that he/she did not ever recall meeting the Pfizer medical representative before and certainly did not recall mentioning any illness to him/her and considered that the statement was inaccurate.

The complainant did not feel that at any stage of the consultation, the representative recognised that he/she was becoming irritated despite the fact that the complainant clearly told the representative that it was not his/her role to question the complainant's clinical judgement. The complainant stated that he/she mentioned all the extra-articular manifestations of seronegative spondyloarthroapthies, not just uveitis and queried why the represenatives manager did not stop the representative at that point and why the representative felt the need to return to the discussion about extra-articular manifestations of psoriatic disease if he/she was aware of the complainant becoming irritated on the first occasion. The complainant felt that his/her clinical judgment was being questioned and that there was no indication from the representative that he/she recognised that the complainant was irritated with him/her during the consultation. The complainant alleged that the representative continued to push the same subject rather than change topics.

The complainant disagreed that he had ever discussed any patient with an infection on monoclonal antibody with the representative and therefore could only assume that she was lying to cover his/her back. The complainant believed that it was a complete fabrication which appeared to question his/her honesty, integrity and professionalism which was of grave concern. The complainant stated that he/she had only ever had one patient on golimumab (for a completely separate indication and they remained well) and had no one admitted to ITU on any biologic therapy since starting work at his/her hospital in September 2012. The complainant could not recall ever meeting the representative but agreed to the meeting as he/she previously knew and had a good working relationship with the representative's sales colleague. The complainant reiterated that he/she had no recollection of meeting the representative in April 2013 and got the impression that he/she was trying to show off to his/her line manager throughout the consultation.

The complainant stated that at no point during or subsequent to the consultation had he/she had an apology from the representative or his/her manager.

The complainant agreed that the representative inroduced his/her manager and he/she did not raise any objections when asked if he/she was happy for the manager to remain in the call. However, the complainant stated that he/she was not forewarned that the representatives manager would be present.

The complainant stated that overall the response from Pfizer had many inaccuracies and after reading it believed that the represenative had lied to try and cover his/her back. The complainant considered that this had taken it past a simple difference in opinion as suggested and his/her honesty, integrity and professionalism had now been brought into question as he/she had never discussed individual patients with any pharmaceutical representative. The complainant considered that the response received from Pfizer was nebulous and did not offer an apology from the representative or their manager. The response stated that Pfizer 'were sorry for the distress' that the complainant had experienced as a result of the consultation but in the complainant's view this was not an apology or an admission that its representatives were in the wrong.

FURTHER COMMENTS FROM PFIZER

In response to a request for further information, Pfizer submitted that there were five entries in its CRM system for interactions between the complainant and its sales representative; the first record dated 3 March 2013 confirmed an appointment was booked with the complainant for a future face to face meeting; the second record dated 18 March 2013 was the record of that meeting, the

objective of which was documented and provided. The third record dated 9 April 2013 detailed a group meeting which both the complainant and representative attended; the fourth record dated 27 September was of a similar nature. The final record was the meeting that took place on 16 January which was the subject of the complaint. In addition, the representative submitted that he/she met and spoke to the complainant in his/her office (shared with a colleague) on 20 November 2013, a screen shot for this meeting was provided.

PANEL RULING

The Panel noted that there were differences in the parties' accounts of what happened during the meeting and other information provided; it was extremely difficult in such cases to know exactly what had transpired. The complainant bore the burden of proof on the balance of probabilities. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually required before an individual was moved to complain. The Panel noted Pfizer's submission that the meeting in question took place on 16 January 2014. The complaint was received in May 2014. The Panel noted that the complainant agreed that he/she had not raised any objections when the representative introduced his/her line manager and queried if he/she could remain in the call. However, the complainant stated that he/she was not forewarned that the line manager would be present.

The Panel noted that the complainant stated he/she felt extremely uncomfortable when the representative enquired about his/her health problem as it was a private issue and the complainant could not recall ever meeting the representative before or mentioning any illness to him/her. The Panel noted Pfizer's submission that the complainant had previously mentioned his/her illness to the representative and therefore he/she considered it appropriate and courteous to ask about it before talking about Enbrel and in the representative and his/her manager's view the complainant engaged in the discussion and did not appear to be uncomfortable. The Panel did not know what had been said by each party regarding the complainant's health issue. The Panel considered that whilst a general enquiry from a representative about a personal health issue might be appropriate and courteous, for a representative to initiate a detailed conversation about a personal medical matter might not be so and particularly when others were present.

Pfizer submitted that with regard to the patient on ITU, the representative stated that the case was previously disclosed by the complainant when they met in April 2013 and at no point did the representative have any personal information about the patient. The complainant disagreed that he/she had ever discussed any patient with an infection on monoclonal antibody with the representative and had no recollection of the April 2013 meeting. The Panel noted that the interaction between the repesentative and the complainant in April 2013 was, according to Pfizer's call records, at a group meeting that both had attended rather than a one to one call.

The Panel noted Pfizer's submission that whilst the representative recognized that on two occasions the complainant was irritated by his/her approach, he/she quickly broadened the discussion or changed the subject in an attempt to de-escalate the situation. The complainant, however, submitted that in his/her view there was no indication that the representative recognised that he/she was irritated during the consultation and queried why the representative felt the need to return to the discussion about extra-articular manifestations of psoriatic disease if he/she was aware of the complainant becoming irritated on the first occasion.

The Panel noted the complainant's allegation that the representative had questioned his/her clinical judgment. The Panel noted that Clause 8.2 required that health professions and the clinical and scientific opinions of health professionals must not be disparaged. The Panel noted Pfizer's submission that in the course of a meeting between a company representative and a health professional it would not be unusual to discuss a clinician's prescribing strategy or appropriately challenge a clinician's prescribing strategy with fair and balanced information to suggest reasonable alternative prescribing decisions.

The Panel noted that the complainant stated that he/she had not discussed any patient with an infection on a monoclonal antibody. The only one patient the complainant had ever had on golimumab remained well and the complainant stated that he/she had had no one admitted to ITU on any biological therapy since he/she had started working at the hospital. The Panel noted that according to Pfizer the complainant and representative had attended a meeting in April where the discussion about the patient in ITU took place. Pfizer had not commented further on the complainant's statements in this regard. The Panel considered that the health professional would know what had happened to his/her patients.

Companies and representatives had to maintain high standards. The Panel noted that it was unfortunate that the complainant was upset by the interaction, nonetheless, it considered that there was no evidence before it to indicate on the balance of probabilities that the two elements of the discussion referred to by the representative were such as to disparage the complainant. It was impossible to determine where the truth lay. The Panel thus ruled no breach of Clause 8.2. This ruling was appealed by the complainant.

The Panel noted the differences between the accounts which involved one person's word against another. It also noted the cumulative effect of the matters raised by the complainant. The Panel considered however that there was not sufficient evidence to show that on the balance of probabilities that either the representative or the company had failed to maintain high standards; no breach of Clauses 9.1 and 15.2 were ruled. The Panel noted its rulings above and consequently ruled no breach of Clause 2. These rulings were appealed by the complainant.

APPEAL FROM THE COMPLAINANT

The complainant stated that whilst he/she still had multiple concerns about the consultation (previously detailed) and appreciated the Panel's ruling that there were '…differences between the accounts which involved one person's word against another', the main issue was the Pfizer sales representative's suggestion that the complainant had previously discussed a patient with the representative who was on a competitor's medicine. The complainant considered that this suggestion questioned his/her professionalism, honesty and integrity.

The complainant alleged that the representative initially stated that he/she had mentioned 'during a previous call in April' that he/she had had a patient who was talking golimumab who had ended up on ITU with 'problems with infection'. The representative also stated that 'he/she was sorry' if the complainant had been irritated by the discussion. The complainant noted that he/she had never received an apology from the representative or his/her manager. From the Panel's ruling, the complainant noted that the representative stated that the initial discussion actually took place at a group meeting rather than at a one-to-one call.

The complainant stated that he/she had only had one patient on golimumab whilst working at his/her hospital (the complainant provided an anonymised list of patients on golimumab registered to his/her hospital) and that patient was on golimumab for a different indication and was started on it in January 2014. The department had only had 12 patients on golimumab and, after reviewing their notes, none appeared to have been admitted to ITU. None of the complainant's colleagues could recall this 'admission'.

Furthermore, since starting at the hospital the complainant had had 2 patients admitted to ITU; one in February 2014 with a completely different illness and not on golimumab and one in March 2013, again with a completely different illness and not on golimumab (the complainant provided details of patients treated and admissions to ITU). The complainant had no idea why the representative came up with his/her suggestion that the complainant had discussed such a patient with him/her and could only conclude that he/she had fabricated the story.

The complainant agreed with the Panel's statement that 'The complainant bore the burden of proof on the balance of probabilities' and that 'extreme dissatisfaction was usually required before an individual was moved to complain' and that the complainant '… would know what had happened to his/her patients'. The complainant hoped that the extra evidence that he/she had provided would help resolve this case satisfactorily. The complainant submitted that the time and stress taken to follow up this complaint demonstrated how upset he/she was with the situation.

The complainant stated that he/she had had hundreds of interactions with representatives in his/her career and had never previously felt the need to complain. The complainant noted the Panel's observation that '… the meeting in question took place on 16 January 2014.' and that 'The complaint was received in May 2014'. This delay was purely because the complainant approached Pfizer first (the complainant contacted the representatives manager on the day of the meeting and then formally complained on 17 January) and he/she was awaiting its response. The complainant alleged that Pfizer's response (letter dated 2 May from a senior Pfizer director, copy provided) was inaccurate as there was no admission that the representatives were in the wrong and no apology (other than sorry for any distress caused). The complainant also provided correspondence that he/she had had with Pfizer previously (letter dated 21 February from the investigating manager at Pfizer).

The complainant alleged that he/she had never and would never discuss an individual patient or his/her case with any representative in any situation whatsoever, particularly at a group meeting, and the representative's suggestion that he/she had, reflected very poorly on the complainant and therefore he/she had taken the matter further. The complainant submitted that if he/she had received an adequate apology from the representative and/or his/her manager at any point, with an acknowledgement that they were in the wrong, then this case would not have been escalated.

COMMENTS FROM PFIZER

Pfizer noted the complainant's reasons for appeal and that there was little mention of some of the topics of the original complaint. As such Pfizer restated its response to the initial complaint. Pfizer also recognized that additional evidence had been submitted and it would also address a number of the comments raised by this correspondence.

Summary of Response To The Original Complaint

Pfizer stated that in its view, although the meeting between the complainant and its representative and his/her manager was a difficult interaction, this case did not represent a breach of Clauses 2, 8.2, 9.1 and 15.2.

Pfizer submitted that with respect to Clause 8.2, at no time during the call was the complainant's scientific or clinical opinion disparaged. Pfizer stated that its representative clearly recognized that on the two occasions that the complainant became irritated by his/her approach, he/she quickly broadened the discussion or changed the subject in an attempt to de-escalate the situation. The representative did not claim or state that the complainant was incorrect or that the complainant's clinical or scientific opinions were unfounded. Pfizer submitted that the representative merely provided an alternative interpretation of the relative importance of uveitis in the clinical decision making process based on the overall efficacy and safety profile of Enbrel and the interpretations of other experts in the field. As such Pfizer did not believe that the representative's actions or those of his/her manager were in breach of Clauses 8.2 or 15.2.

Pfizer submitted that although the representative referred to a previous conversation about a patient on ITU, it did not believe that this was evidence of a breach of Clause 15.2. The representative never had any personal information about the patient. The representative did not hear about the patient from any source other than the complainant at their previous meeting. Similarly the representative raised the competitor medicine not to disparage it or the complainant's clinical approach, but to highlight where etanercept might be an alternative medicine due to its different pharmaceutical properties eg half-life.

With respect to the concern that the representative was over familiar with the complainant in the preliminary part of the call, Pfizer noted that the representative only referred to his/her previous illness in the context of inquiring about his/her wellbeing. As the complainant had discussed this previously with the representative it was appropriate and courteous to ask how he/she was; the complainant did not express a wish to change the subject and actively engaged in the discussion. Pfizer recognized that there was a line between over familiarity and professional courtesy, however the representative's actions did not represent a breach of the high standard of ethical conduct in the discharge of his/her duties, and as such Pfizer denied a breach of Clause 15.2. Furthermore, as previously described, the representative had met the complainant several times before so a certain level of familiarity was acceptable. Pfizer stated that it took the complainant's complaint very seriously, and immediately following its receipt, it embarked on an internal investigation into the conduct of its representative and their manager. The investigation did not find any evidence of serious misconduct or breaches of the Code.

Pfizer submitted that with regard to Clause 9.1 and 2, it provided relevant briefings and guidance to its representatives on the appropriate conduct it expected of them. Additionally Pfizer had ensured that its representatives were briefed on the appropriateness of content to be recorded in its CRM system as previously described. Similarly Pfizer made it a priority to ensure that its representatives were trained appropriately on the materials that they used and both the representative and their manager were up-to-date with their relevant training. Pfizer did not consider that it had failed in its responsibilities to maintain high standards and as such it had not brought discredit to, or reduced confidence in, the pharmaceutical industry.

Response To The Appeal

Pfizer submitted that the complainant's main issue was that his/her professionalism had been brought into question by the representative's suggestion that together they had previously discussed a patient who was on a competitor's medicine. While Pfizer acknowledged that while the complainant might consider this to be so, it did not believe that this equated to a breach of Clause 8.2, namely that the complainant's clinical and scientific opinions had been disparaged. It was not uncommon for health practitioners to share anonymised, clinical vignettes with representatives to illustrate some of the nuances of clinical decision making. Pfizer did not consider that such educational discussions called a health practitioner's integrity or professionalism into question. For the avoidance of doubt, Pfizer had never had any cause to debate the complainant's professionalism, honesty or integrity.

Pfizer noted the complainant's submission that he/she had never received an apology from the employees at issue following the face-to-face meeting on 16 January 2014. Pfizer noted that its letter of 2 May to the complainant, stated 'We are sorry for the distress that you experienced. It was not our representative and his/her manager's intention to cause any anxiety or distress'. Pfizer's letter also highlighted that as both employees had acted on behalf of the company that this apology should come from the company. Pfizer also noted that it had taken the complainant's complaint seriously. Pfizer had commenced a thorough internal investigation within 28 days of receipt of the complaint. Evidence of this was provided as an attachment to the complainant's appeal (Pfizer letter dated 21 February from its investigating manager). The complainant stated 'I can honestly say that I can't recall any previous interactions with [the representative or his/her manager] in the past'. This statement was in contrast to Pfizer's CRM records previously provided which showed at least three previous meetings between the representative and the complainant before the call on 16 January 2014. Pfizer considered that the anonymised list of patients on golimumab dated 28 July 2014 and the anonymised undated chart of patient admissions provided by the complainant with his/her appeal supported the Panel's observation that 'The Panel considered that the health professional would know what happened to his/her patients'. Pfizer did not consider that this data should impact on the appeal as it merely provided consistency with the Panel's previous stance that the representative had not disparaged the complainant's clinical or scientific opinion and as such was not in breach of Clause 8.2.

Pfizer recognized that there were significant discrepancies between the complainant's account and that of its representatives. However, Pfizer challenged the complainant's assertion that its representative 'fabricated' the story regarding the ITU patient. The representative had repeatedly stated that this clinical case was shared when he/she met the complainant in April 2013 (a meeting documented in Pfizer's CRM). Pfizer took these internal investigations very seriously and noted that an employee who was knowingly not truthful would be in breach of its internal disciplinary procedure. Such a breach would represent gross misconduct and might result in summary dismissal, in line with Pfizer's disciplinary policy. As such Pfizer challenged the assertion that the representative had knowingly fabricated a story and re-told it in the course of an internal investigation while also being aware of the potential severity of the consequences.

Pfizer again formally apologized for the anxiety and distress caused to the complainant by this interaction. Similarly, Pfizer stood by its previous apology made to the complainant, both verbally and

in writing by senior staff throughout the time from the initial complaint in January through to its letter to the complainant in May 2014.

FINAL COMMENTS FROM THE COMPLAINANT

There were no further comments from the complainant.

APPEAL BOARD RULING

The Appeal Board considered that the complainant had provided evidence to show that the patient in ITU on golimumab that he/she was purported by the Pfizer representative to have discussed did not in fact exist. The Appeal Board noted from the complainant that this was the focus of the appeal as the disputed, on a point of principle, the representative's submission that he/she had ever discussed any of his/her patients with any medical representative. The complainant stated at the appeal that he/she could find no records in his/her or his/her secretary's diary to correlate with Pfizer's CRM entries for meetings he/she was stated to have previously had with the representative. The complainant could not recall previously meeting the representative or his/her manager before the meeting at issue in January 2014. The complainant acknowledged that he/she might have seen them at some point but could not recall a meeting. Any meeting would have been limited to a greeting; he/she had not sat down and talked to them. The complainant also stated that the nature of his previous illness was well known amongst his department and thus the representative might have easily found out about it from other staff. The Appeal Board noted that the complainant had stated that he/she had a good working relationship with another Pfizer representative.

Those representing Pfizer at the appeal submitted that the company was satisfied that the representative had had a discussion about the ITU patient in question as that was what he/she had stated consistently in its investigation. The Appeal Board was extremely concerned that those representing Pfizer at the appeal confirmed, in response to questioning, that the company had not re-interviewed the representative or his/her manager in light of the new evidence provided in the appeal (lists of patients on golimumab and admissions to ITU) because its internal investigation had closed in March. This was despite the fact that the company agreed that the new evidence suggested that the ITU patient did not exist and that the prior meeting might have been misremembered or not happened. The Appeal Board was concerned that Pfizer had not questioned its representative or his/her manager to establish whether he/she had mistaken the complainant for a different doctor in a different hospital or had, in fact, fabricated the previous interaction. Either way the Appeal Board considered that on the balance of probabilities, it was satisfied that the representative had not discussed a patient in ITU on golimumab with the complainant in April 2013.

The Appeal Board noted that the representative's CRM entry for the meeting in April 2013, at which he/she stated she had discussed the patient in ITU with the complainant, did not include any notes about the meeting. Indeed, of the five meetings recorded between the representative and the complainant only one CRM entry had a note. The complainant disputed the representative's submission that he/she attended a further meeting between him/her and a colleague with whom he/she shared an office. The Appeal Board considered that Pfizer should have explored the lack of CRM notes. The Appeal Board was concerned that the meeting at which the representative claimed to have first discussed a patient in ITU on golimumab with the complainant was nine months before the meeting at issue in January 2014 and yet, without any call notes to refer back to, the representative had managed to recall detailed information about that discussion.

The Appeal Board noted from the complainant and the notes of the manager that there were no raised voices during the meeting in January; this did not correlate with Pfizer's response in which it stated that the complainant had raised his/her voice. The manager's notes referred to the representative's mention of a patient with infection issues who the complainant had discussed with the representative at a previous call. The Appeal Board noted that Pfizer recognized that there were significant discrepancies between the complainant's account of the meeting in January and that of the representative and manager.

The Appeal Board noted from the complainant that had the representative or his/her manager apologised for the representative's actions he/she probably would not have complained. The Appeal Board noted that both parties agreed that the meeting had not gone well and yet Pfizer had only apologised for distress caused to the complainant and not about the conduct of its representatives which it submitted was acceptable even in light of the new evidence provided in the appeal.

The Appeal Board noted the complainant's submission that he/she never discussed his/her patients with medical representatives. The Appeal Board considered that, given the evidence before it, on the balance of probabilities, in April 2013 the representative could not have discussed with the complainant one of his/her patients who was on golimumab and admitted to ITU as such a patient did not exist within the complainant's hospital either then or since; the reference to such a discussion at the meeting in January 2014 was thus unacceptable. The Appeal Board considered therefore that the representative had failed to maintain a high standard of ethical conduct; a breach of Clause 15.2 was ruled. The appeal on this point was successful. Noting this ruling and its comments above the Appeal Board also considered that Pfizer failed to maintain high standards and it ruled a breach of Clause 9.1. The appeal on this point was successful.

The Appeal Board noted at the appeal that the complainant indicated that the appeal did not relate to the alleged disparagement. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 8.2. The appeal on this point was unsuccessful.

The Appeal Board did not consider that the circumstances of this case warranted a ruling of a breach of Clause 2 and it upheld the Panel's ruling in that regard. The appeal on this point was unsuccessful.

Complaint received **8 May 2014**

Case completed **7 November 2014**

ANONYMOUS PHARMACIST v LILLY

Nurse Education Service

An anonymous, non-contactable practice pharmacist alleged that a medical education programme offered by Eli Lilly and Company was a thinly disguised method of promoting products and its implementation had been unprofessional.

The complainant noted that the programme was sold as a mentorship scheme to help local practice nurses manage diabetes. An independent company provided the nurses. The complainant considered that the company's name, which was a play on NHS lettering, was odd and looked like passing off.

The complainant described how a representative had arranged a meeting at his/her practice with the lead diabetes GP and nurse to explain the service; in reality the meeting was arranged merely to fill out a form to take some IT information and to book an appointment for the nurse to visit. It was clear that the representative had 'attached' him/herself to the educational programme. It was made clear that the representative was there in a non-promotional capacity and did not discuss product. A couple of days later, however, the representative returned to make appointments to discuss products despite knowing the practice's robust policy for seeing representatives. The practice manager naively felt obliged to agree to a meeting due to the service being offered. The complainant was concerned that the representative had obtained a number of contacts within the practice on the back of delivering an educational service including a sales presentation in a very short time period. Such behaviour did the industry no credit.

The complainant noticed a significant increase in the use of Lilly's diabetes medicine and referred, *inter alia*, to a series of tutorials run by the service nurse which each ended with a very positive message for the Lilly product relative to the alternatives. In addition, the practice nurse felt that she had been overwhelmed by requests to see the Lilly representative. The complainant considered that his/her practice had been 'targeted' during the service and described similar events and an increase in the use of Lilly products at other local practices as a disgraceful trend.

The detailed response from Lilly is given below.

The Panel noted that the complainant was anonymous and non-contactable. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties. The complainant had the burden of proving his/her complaint on the balance of probabilities.

The allegations concerned not only what happened at the complainant's surgery but also a broader allegation about local implementation of the service. The complainant had not identified his/her surgery, although he/she had identified the region. It was not possible to contact the complainant for further information.

The Panel noted that the Enhanced Management of Diabetes (EMD) service was described as a clinical mentorship programme to support confidence and capability in managing type 2 diabetes. According to the EMD service detail aid, the service aimed to support the diabetes quality outcomes framework as part of the quality, innovation, productivity and prevention (QIPP) agenda; for the diabetes specialist to support appropriate referrals and patient care; and for the primary care health professional to build confidence and capability in managing type 2 diabetes.

The Panel noted that representatives briefly introduced the service to practices at a promotional call. Subsequently at a non-promotional call the representative would present the service and complete the Practice Authorisation Form which had to be signed by two GPs. The representative then set up the initial meeting with the service nurse who thereafter ran the service. The EMD service was anticipated to require approximately 5 service days to deliver in an average 3 GP practice.

The service comprised four steps. Firstly, patients were selected who would benefit from review to improve health outcomes. Subsequently, there was a patient review meeting which comprised training and a case note review of suboptimally controlled patients in line with national guidelines. The nurse delivered a tailored clinical mentorship programme on the management of type 2 diabetes which comprised training modules chosen by the practice according to need. The final section of each module discussed relevant medicines. It did not appear that any module gave disproportionate emphasis to Lilly products or ended with a very positive message for such products as alleged.

At patient review meetings the practice diabetes team identified suboptimally controlled patients who should be invited for clinical review. The EMD service Nurse Brief referred to the GP's clinical assessment of each patient and him/her deciding which form of treatment or non-medical intervention would be most appropriate for that patient. The GP had to sign the Practice Treatment Protocol. The service nurse could not write prescriptions, recommend a specific medicine or implement a switch service. The EMD Nurse Brief explained that following the case notes review individual patients should be allocated to one of the following: education and counselling; oral therapy; glucagon-like peptide-1 (GLP-1) agonists and insulin therapy. Each intervention would only be decided following a face-to-face consultation and clinical assessment to establish whether the patient had received

maximum benefit from his/her current regimen. Educational and lifestyle counselling would be provided in isolation of any other intervention.

Identified patients were then invited to a clinic attended by the service nurse, practice nurse or GP. The EMD service Nurse Brief explained that the role of the service nurse was to support and mentor the nominated member of staff. A detailed clinic assessment sheet for each patient consultation was presented by the practice nurse/GP to the lead GP to authorise action in alignment with treatment protocol.

The Panel noted the complainant's allegation that the name of the third party service provider played with NHS lettering and thus looked like passing off. The Panel accepted that the name of the third party provider was not wholly dissimilar to NHS but did not consider that the complainant had provided any evidence to establish that health professionals had been confused or otherwise misled by the name of the organisation. No breach was ruled.

The Representative EMD Service Briefing Document made clear that representatives could only provide administrative support in relation to service delivery and that support of a project must not be dependent on the customer prescribing specific medicines. Prescribing of specific products must not be linked to the service either in conversation or in writing with any customer. One page discussed the practice authorisation form and stated 'Networking key personnel within the practice, by the Lilly/[named pharmaceutical company] representative, to ensure an understanding and commitment to the EMD service has been achieved will enable the service to be implemented in a timely and efficient manner'. In response to the statement 'I don't want lots of representatives coming to see how I'm getting on with the programme!' the representatives' Q&A document explained that the representative's role was 'purely administrative and to guide you through the Authorisation Documentation. All other discussions in relation to service provision should be held between you and the Service Nurse Advisor'.

The EMD representatives' training slides included a section themed 'Working Ethically with Nurse Support Programmes', within which a slide stipulated, *inter alia*, 'Keep any promotional activity separate from EMD discussions. A separate customer meeting should be made to discuss EMD', 'Do not work in any EMD practices within 24 hours of the EMD nurse advisor working there' and 'Ensure EMD plans are separated from any business plans'. A subsequent slide headed 'Maintain your account' advised 'Call in and ask if they are happy with the service, do they need any further support (not 24 hours either-side of a service day)'. Such guidance regarding the '24 hour rule', contrary to Lilly's assertion was not clearly stated in the representatives' briefing guide. In the Panel's view companies should be mindful of the impression given by the presence of the representative at the practice during the provision of the service. The Panel considered it would be helpful if there was detailed written guidance on the acceptability or otherwise of promotional calls during the period of time that the EMD service was provided and was particularly concerned that in the absence of such guidance representatives were encouraged to visit practices during the provision of the service as long as the visit was more than 24 hours either side of the nurse advisor working there. The Panel queried whether this, in conjunction with the direction to network at the practice, might result in a practice not fully understanding the difference between the representatives' promotional and non-promotional roles.

The Panel noted Lilly's submission about the number of calls by representatives in relation to Lilly's medicines at the practices that underwent the EMD service between 2012 and 2014. The Panel was extremely concerned that no representative EMD service calls were recorded from 2012 – 2014 despite the implementation of 9 services. Lilly estimated a minimum of 3 such calls per practice. The Panel therefore queried how reliable the recorded call rates were generally. In addition it appeared that Lilly did not record telephone requests for visits which in the Panel's view was unusual.

Whilst the Panel had concerns about the management of representatives, in particular the failure to record any local service calls as set out above, it also noted its comments above about the burden of proof. The complainant's surgery had not been identified and thus it was not possible to determine precisely what had occurred there. Similarly it was not possible to determine precisely what had occurred within the region. In such circumstances the Panel ruled no breach of the Code in relation to the conduct of the representative.

The Panel noted the complainant's allegation that the service nurse provided biased education and the service led to a disproportionate prescribing of Lilly/[named pharmaceutical company] products. The Panel noted the details of the EMD service and its comment above that it did not appear that any module gave disproportionate emphasis to Lilly products as alleged. The Panel noted that the Code stated that service providers must operate to detailed written instructions provided by the company similar to the briefing material for representatives. The Panel was concerned about the failure to provide any formal briefing to the service nurses on how the training modules were to be used within GP practices. This was especially so given the modules discussed products. The Panel noted Lilly's submission that the service nurses were 'independent diabetes specialists who trained themselves on the module'. The Panel had no way of knowing what was said by the service nurses during the training sessions.

The Panel noted its general comments and concerns about the service but bore in mind that the complainant had to establish his/her case on the balance of probabilities. On balance the Panel did not consider that there was sufficient evidence to establish whether, either at the complainant's surgery or elsewhere locally, the service had been offered in connection with the promotion of medicines or otherwise as an inducement contrary to the Code; no breach was ruled. Similarly the Panel

did not consider that there was evidence to show that the EMD service was a disguised promotional activity; no breach of the Code was ruled.

The Panel noted its general comments above about the service. Whilst some concerns were outlined above the Panel did not consider that there was any evidence before it to demonstrate that the service as implemented in the complainant's surgery or elsewhere in the region was biased towards Lilly products as alleged. Consequently the Panel ruled no breach of the Code.

Noting its rulings above, the Panel ruled no breaches of the Code including no breach of Clause 2.

An anonymous, non-contactable complainant who described him/herself as a practice pharmacist complained about a medical education programme offered by Eli Lilly and Company Ltd.

COMPLAINT

The complainant explained that from local discussions about the programme he/she was concerned that it was a thinly disguised method of promoting products and represented a very serious breach of the Code.

The complainant stated that an arrangement with two local primary care trusts (PCTs), which were now clinical commissioning groups (CCGs), was made with the local Lilly sales manager for the Lilly nurse education service to be offered to practices. It was sold as a mentorship scheme to support local practice nurses in managing diabetes. An independent company provided the nurses. The complainant considered that the name of the company was a play on NHS lettering which was odd and looked like passing off. The complainant stated that on paper it looked like a useful education service, however the implementation had been very unprofessional and showed that the pharmaceutical industry had not changed at all. That was the complainant's experience and from discussions with local colleagues, it was repeated locally.

The complainant explained that a representative had called into the practice, asked to see the practice manager and stated that he/she worked on behalf of the then PCT to deliver diabetes training. The representative asked the manager to arrange a meeting with the lead diabetes GP and nurse to explain the service. The complainant was invited to attend the meeting and stated that in reality the meeting was arranged merely to fill out a form with the doctors' names and numbers, to take some IT information and to book an appointment for the nurse to visit. Such information could have been obtained from the practice manager but it was clear that the representative had 'attached' him/herself to the educational programme. It was made clear that the representative was there in a non-promotional capacity and did not discuss product.

However, a couple of days later the representative returned and asked to see the practice manager who assumed it was in relation to the programme; it was actually to request appointments and meetings with the practice to discuss products. The complainant stated that as the practice had a robust policy for seeing representatives which the representative was aware of, it was clear that the programme was being misused to secure a promotional opportunity. The complainant was convinced that this must be outside the 'spirit' of the Code. The practice manager naively felt obliged due to the service being offered and agreed to set up a meeting which caused disruption at the practice now that the manager understood how the representative had behaved.

The complainant was concerned that the representative had managed to obtain a number of contacts within the practice on the back of delivering an educational service leading up to and including a sales presentation to those people in a very short time period. The complainant alleged that it was disgraceful behaviour and did the pharmaceutical industry as a whole no credit.

The complainant stated that worse followed. In a routine review of the practice's prescribing data, he/she noticed a significant increase in the use of Lilly's medicine for diabetes. Previously the practice had a reasonable distribution of products as its formulary recognised the need to offer a wide range of alternatives, particularly insulin.

The complainant stated that on speaking with the practice nurse, it became clear that the service nurse had guided the practice nurses towards Lilly's medicines. The service nurse ran a series of tutorials with slides on aspects of diabetes. In every case, the scenario ended with a very positive message for the Lilly product relative to the alternatives. The complainant alleged that this biased education had led to medicine selection that favoured Lilly and he/she understood from a representative of a competitor company that there had been extensive inter-company discussions about this issue.

In addition to the service nurse activity, the practice nurse felt that she had been overwhelmed by requests to see the Lilly representative as well as those from the other named pharmaceutical company which co-sponsored the programme. The complainant considered that his/her practice had been 'targeted' by the sponsoring companies during the service nurse activity.

The complainant was sure that the Authority would review the number of visits made by representatives to practices which had used the service nurse service and was equally sure that it would exceed what the Code considered acceptable.

The complainant stated that having spoken with colleagues in other practices, multiple visits by representatives to set up an education service, rapid follow-up opportunities to sell products, almost carpet bombing practices whilst the nurse was working, biased education, advice from the service nurse and a disproportionate increase in the prescribing of Lilly diabetes products seemed to be a trend which was absolutely disgraceful.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 7.2, 9.1, 12.1, 15.2, 15.3, 15.4, 18.1 and 18.4 of the Code.

RESPONSE

Lilly explained that the nurse education service referred to was the Enhanced Management of Type 2 Diabetes (EMD) training programme initiated in 2012 in the locality of the complainant's practice until March 2014. The service was undertaken on behalf of Lilly by an independent company. In 2012 it was co-sponsored by Lilly and another pharmaceutical company. Subsequently and until its completion it was sponsored by Lilly.

Lilly submitted that the complaint lacked important information that would have allowed it to identify the alleged behaviour complained about; there were no specific dates or practice locations identified, although it was clearly sited in a named region. Lilly stated that any further information about the alleged behaviour would be helpful.

Lilly submitted that the EMD service was a UK wide service run in GP practices throughout the UK. Lilly was very disappointed to receive a complaint about the service as it took its obligations under the Code very seriously. Lilly conducted an investigation and refuted all allegations of improper conduct or Code breaches as alleged by the complainant.

Lilly submitted that it had a business relationship with the named CCGs. Lilly's healthcare development manager (HDM) spoke with various members of the local CCGs in the course of her business. These calls could be about Lilly service offerings such as the EMD service, or about its medicines. None of the calls were about service offerings and Lilly medicines. During 2012-2014, the HDM recorded 64 calls to 30 individuals at the named CCGs, 35 of which were about service offerings including the EMD service, 29 were about Lilly medicines.

The EMD service was a clinical mentorship programme designed to support confidence and capability development in the management of type 2 diabetes in primary care. Nine local practices received the EMD service during 2012-2014.

As set out in the EMD service leavepiece, the EMD service detail aid, the EMD service included four parts as follows:

1 Patient selection for clinical review using data collection software.

2 Case notes review from patients identified at stage 1. A tailored education and training programme using the EMD service modules. These modules were optional and practices selected the modules that they identified as being relevant to them. The optional tailored education consisted of 4 modules:

- Module 1 Oral Optimisation, focussed on applying National Institute for Health and Care Excellence (NICE) guidelines and optimising all therapies,
- Module 2 Beyond Oral Therapies, focussed on principles of management following failure of oral therapies,
- Module 3 Early Insulin Usage, focussed on maximising the first step in insulin therapy,
- Module 4 Insulin Optimisation, focussed on maximising glycaemic control in patients suboptimally controlled on insulin.

3 Joint diabetes clinic when a nominated practice nurse conducted a diabetes review clinic supported and mentored by the service nurse.

4 Pre/post practice report with key indicators, the EMD service practice report was completed by the service nurse advisor stating what had been done.

The representative referred a practice for an EMD service to the service organisation and then provided only administrative support. This support involved guiding the health professional through the authorisation documentation and setting up the meeting with the service nurse. This was clearly stated and outlined in the representatives' briefing document and the EMD Nurse Brief. Following a practice referral by a representative and setting up the initial meeting, all other discussions in relation to the service provision were held between the health professional and the service nurse.

In the representatives' briefing document, it was clearly stated that the representative could only provide administrative support in relation to service delivery. It was also stated that the support of this project must not be dependent on the customer prescribing a Lilly product. The prescribing of specific products must not be linked to the service either in conversation or in writing with any customer. In addition, it clearly stated that a detailed discussion about the EMD service could only take place during a non-promotional call and must not be instigated at the same time as a call at which products were promoted.

The Lilly representative completed the practice details on an EMD service Practice Authorisation Form, obtained signature(s) and then scheduled a meeting between the practice and a service nurse usually whilst in the identified surgery in the presence of the practice manager.

The service nurse's responsibilities were set out in the EMD Nurse Brief. The nurse advisor could not and was not allowed to write prescriptions, recommend a specific medicine, or implement a switch service. Service nurse advisors were bound by their ethical obligations.

The HDM in question worked for Lilly during 2012-2014. Her role included liaising with commissioning groups, including those in the named region. The HDM had no direct involvement with the setup or delivery of the service.

The EMD service was one service run nationally and thus there was no local representatives' training material. Representatives were provided with the representatives' briefing document, a Q&A

document and the EMD service material, ie the EMD service leavepiece and the EMD service detail aid.

Nationally representatives could introduce the EMD service to relevant healthcare providers as outlined in the representatives' briefing document, the EMD service leavepiece and the service detail aid. If a practice was interested in the EMD service then it could be signed up as described above. The way practices chose to take various parts of the EMD service was described above.

Lilly recognised that to successfully manage diabetes, health professionals and patients needed support to address the daily challenges of diabetes. Lilly appointed the service organisation to supply the EMD service in 7 February 2012. It was a respected company providing nurse services to third parties such as Lilly. Copies of relevant material provided by the service organisation and Lilly about the EMD service were provided.

The implementation of the EMD service was described in the nurse brief in a full page service process flow diagram showing responsibilities and activities.

The service organisation maintained records of practice staff who participated in the EMD service. This information was not shared with Lilly. The EMD service was provided by the service organisation entirely without involvement or influence by Lilly. The GP practices identified their own staff to participate in the EMD service.

Lilly representatives had all passed the ABPI Medical Representatives' Examination and were only instructed to make calls as outlined in Clause 15. If a call was about the EMD service then the procedure as described in the representatives' briefing document must be followed.

During 2012-2014, all the calls recorded, concerned Lilly medicines not service offerings such as the EMD service made by Lilly representatives in 6 of the 9 practices where EMD service was completed locally. In the remaining 3 practices where the EMD service was completed there were no recorded calls concerning Lilly medicines.

Summary

All of the materials relating to the provision of the EMD service were reviewed and certified by company signatories.

The service was clearly identified as being provided and sponsored by Lilly and the other named company. The companies' logos were on materials and the sponsorship position was made clear in all discussions.

In summary, Lilly stated that the EMD service enhanced patient care and benefited the NHS. The provision of the service was strictly non-promotional and not connected with the sale of any individual Lilly products or those of its former co sponsor. Lilly submitted that its representatives and the service provider had not made or implied a link between this service and the companies' products. The EMD service was not a disguised method of promoting products.

For all these reasons, Lilly did not consider that it had brought discredit upon or reduced confidence in the pharmaceutical industry and denied that it had breached Clause 2 or Clauses 7.2, 9.1, 12.1, 15.2, 15.3, 15.4, 18.1 and 18.4.

In response to a request for further information from the Panel, Lilly submitted that the service organisation trained service nurses for the EMD service; there was no specific briefing document on the four training modules. The service nurses were independent diabetes specialists who trained themselves on the modules. Lilly submitted that a newly recruited service nurse could have been trained on the modules by one or more of the more experienced service nurses. Lilly noted that the service organisation refuted the allegation that its service nurse had guided the practice nurse towards Lilly medicines and had provided biased education that favoured the selection of Lilly medicines. The service organisation clearly stated that its service nurse could not and would not write prescriptions, recommend specific products or implement a switch service.

Lilly submitted that the service nurse's role was to mentor and educate the practice on the management of diabetes in line with NICE guidance resulting in improved patient outcomes through optimised care and the four modules were tools used in that task. The modules covered the licensed products within each therapeutic group and had no bias towards any medicine.

Lilly conducted further investigations and confirmed that there was no guidance document on promotional calls to EMD practices whether from national or local senior sales teams or otherwise. Lilly had provided the EMD training slides used for national representatives which instructed representatives not to discuss products during the EMD service call and not to work with a participating EMD practice within 24 hours of the service nurse working there. These instructions were reinforced and clearly stated in the representatives' briefing guide and repeated to representatives on a regional basis by the district sales managers including the named area. Lilly refuted that its representative had used the EMD service to secure a promotional opportunity as alleged.

Lilly gave details of the calls made by the HDM between 2012 and 2014; 29 calls related to Lilly medicines and 35 calls related to services such as the EMD service in local practices. All of these calls were made at the administrative offices of the local PCT.

Lilly submitted that the representative's 29 calls made to the 9 EMD practices during 2012-2014 were all related to Lilly medicines; no EMD service calls were recorded. Lilly assumed, however, that at least 3 calls per practice would have been made, one to

introduce the service, one for information and one follow up call, indicating that another estimated 27 calls were made by the representative for the EMD service. Lilly had no record of telephone requests for such meetings or calls. A summary of the representative's calls was provided.

Lilly explained that there were no recorded calls in relation to service offerings such as the EMD service. In response to a request for further information in relation to each of the 29 calls made by the Lilly representative to the 9 practices within Blackpool & Fylde between 2012 and 2014 Lilly provided the following details:

- practice 1, the EMD service ran January – June 2012, no product calls made
- practice 2, the EMD service ran May – October 2012, two product calls made
- practice 3, the EMD service ran May – February 2013, four product calls made
- practice 4, the EMD service ran January – July 2012, three product calls made
- practice 5, the EMD service ran January – July 2012, no product calls made
- practice 6, the EMD service ran October 2013 – March 2014, no product calls made
- practice 7, the EMD service ran January 2011 – January 2012, no product calls made
- practice 8, the EMD service ran January – July 2012, no product calls made
- practice 9, the EMD service ran May – November 2013, no product calls made.

In conclusion, Lilly stated that its EMD service had enhanced patient care and benefited the NHS. Service provision had been strictly non-promotional and not connected with the sales of any Lilly products. The representatives and the service provider had not made or implied a link between the service and Lilly products.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties. The complainant had the burden of proving his/her complaint on the balance of probabilities.

The allegations concerned not only what happened at the complainant's surgery but also a broader allegation about local implementation of the service. The complainant had not identified his/her surgery, although he/she had identified the region. It was not possible to contact the complainant for further information.

The Panel noted that a named pharmaceutical company had co-sponsored the EMD service with Lilly between January and December 2012. The complainant had referred to that company solely in relation to the number of requests made by representatives from both companies to see the practice nurse at the complainant's surgery during the EMD service. All of the documents provided by Lilly including those given to health professionals and patients still incorporated the other company's name and/or corporate logo. The Panel noted that the case preparation manager had not taken the matter up with that other company at the outset nor on receipt of Lilly's response. The Panel noted that under the Constitution and Procedure it had no power to either refer the matter directly to the pharmaceutical company or request the case preparation manager to do so.

Clause 18.4 provided that medical and educational goods and services must enhance patient care or benefit the NHS and maintain patient care. The relevant supplementary information provided further guidance about the implementation of such services and the limited role of representatives. Representatives could introduce a service by means of a brief description and/or delivering materials but could not instigate a detailed discussion about the service at the same time as a call at which products were promoted. Reference was made to representatives providing administrative support in relation to the provision of a service. The relevant supplementary information made it clear that Clauses 18.1 and 18.4 prohibited switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine was simply changed to another. A therapeutic review which ensured that patients received optimal treatment following a clinical assessment was a legitimate activity for a pharmaceutical company to support.

The Panel noted that the EMD service was described as a clinical mentorship programme to support confidence and capability in managing type 2 diabetes. According to the EMD service detail aid, the service aimed to support the diabetes quality outcomes framework as part of the quality, innovation, productivity and prevention (QIPP) agenda; for the diabetes specialist to support appropriate referrals and patient care; and for the primary care health professional to build confidence and capability in managing type 2 diabetes.

The Panel noted that representatives could briefly introduce the service to practices at a promotional call using the EMD leavepiece. Subsequently at a non-promotional call the representative would present the service using the EMD service detail aid and complete the Practice Authorisation Form which outlined service implementation, contact details and had to be signed by two GPs. The representative then set up the initial meeting with the service nurse who thereafter ran the service. The EMD service was anticipated to require approximately 5 service days to deliver in an average 3 GP practice.

The service comprised four steps. Firstly, patients were selected for clinical review via a data collection search which included a baseline review of all diabetics highlighting those who would benefit from review to improve health outcomes. An initial outcome report was provided to the practice. Subsequently, there was a patient review meeting which comprised training and a case note review of suboptimally controlled patients in line with NICE

guidelines 2009. The nurse delivered a tailored clinical mentorship programme on the management of type 2 diabetes which comprised training modules chosen by the practice according to need. The four available training modules were 'Oral optimisation, Applying NICE guidelines and optimising oral therapies; Beyond Oral Therapies, Principles of management following failure of oral therapies; Early Insulin Usage, Maximising the first step in insulin therapy; and Insulin Optimisation, Maximising glycaemic control in patients suboptimally controlled on insulin'. The first four sections of each module were identical and covered diabetes in the UK, diagnosis criteria, aims of management and managing poor control. The final section of each discussed relevant medicines. It did not appear that any module gave disproportionate emphasis to Lilly products or ended with a very positive message for such products as alleged. Medicines were discussed in relation to relevant NICE guidelines and details of common side effects and contraindications were given. Readers were referred to the products' summaries of product characteristics (SPCs) for further information.

The patient review meeting was attended by the service lead GP and his/her diabetes team to identify suboptimally controlled patients and should be invited in for clinical review. The EMD service Nurse Brief referred to the GP's clinical assessment of each individual patient and him/her deciding which form of treatment or non-medical intervention would be most appropriate for that patient. The GP had to sign the Practice Treatment Protocol which covered patient identification; patient review including an education and training workshop and the role of the service nurse advisor; the nurse clinic process, clinic content and logistics, the NICE treatment algorithm 2009 and an alternative practice treatment algorithm. The selected treatment algorithm had to be signed by the GP. It was made clear that the nurse advisor could not write prescriptions, recommend a specific medicine or implement a switch service. The EMD Nurse Brief explained that the case notes review should result in individual patients being allocated to one of the following treatment arms: education and counselling; oral therapy; glucagon-like peptide-1 (GLP-1) agonists and insulin therapy. Each intervention would only be decided following a face-to-face consultation including a clinical assessment to establish whether the patient had received maximum benefit from his/her current regimen. Educational and lifestyle counselling would be provided in isolation of any other intervention.

Identified patients were invited to a clinic attended by the nurse advisor, practice nurse or GP. The EMD service Nurse Brief explained that the nurse's role was to support and mentor the nominated member of staff as he/she commenced a comprehensive clinic assessment of patients enabling him/her to transition the training received into practical experience of managing patients suboptimally controlled on their current therapies. A detailed clinic assessment sheet for each patient consultation was presented by the practice nurse/GP to the lead GP to authorise action in alignment with treatment protocol. All patients received patient education and counselling from the practice nurse.

The Panel noted the complainant's allegation that the name of the third party provider played with NHS lettering and thus looked like passing off. The Panel noted that the complainant had incorrectly referenced the name of the organisation. The Panel noted that according to the representatives' Q&A document in response to someone stating 'I have never heard of [service company]' representatives were told to refer to the rigorous selection process and explain that it was a healthcare agency which was also an independent service provider to the NHS. The Panel accepted that the name of the service organisation was not wholly dissimilar to NHS but did not consider that the complainant had provided any evidence to establish that health professionals had been confused or otherwise misled by the name of the organisation. No breach of Clause 7.2 was ruled.

The Panel noted the allegation about the conduct of a representative at the complainant's surgery and a general allegation that such conduct was repeated locally. The Panel noted its comments above about medical and educational goods and services and the limited role of representatives as set out in the supplementary information to Clause 18.4 and Lilly's description of the representatives' role.

The Representative EMD Service Briefing Document outlined the service, the roles and responsibilities of the service nurse and the relevant requirements of the Code. It was made clear that representatives could only provide administrative support in relation to service delivery and that support of a project must not be dependent on the customer prescribing a Lilly product. Prescribing of specific products must not be linked to the service either in conversation or in writing with any customer. Page 15 discussed the practice authorisation form and stated 'Networking key personnel within the practice, by the Lilly/ [named former co-sponsor] representative, to ensure an understanding and commitment to the EMD service has been achieved will enable the service to be implemented in a timely and efficient manner'. In response to the statement 'I don't want lots of representatives coming to see how I'm getting on with the programme!' the representatives' Q&A document explained that the representative's role was 'purely administrative and to guide you through the Authorisation Documentation. All other discussions in relation to service provision should be held between you and the Nurse Advisor'.

The EMD representatives' training slides included a section themed 'Working Ethically with Nurse Support Programmes', within which a slide headed 'In a Nutshell' stipulated, *inter alia*, 'Keep any promotional activity separate from EMD discussions. A separate customer meeting should be made to discuss EMD', 'Do not work in any EMD practices within 24 hours of the EMD nurse advisor working there' and 'Ensure EMD plans are separated from any business plans'. A subsequent slide within the section themed 'EMD – A Representative's Perspective' was headed 'Maintain your account' and advised 'Call in and ask if they are happy with the service, do they need any further support (not 24 hours either-side of a service day)'. Such guidance regarding the '24 hour rule', contrary

to Lilly's assertion was not clearly stated in the representatives' briefing guide. In the Panel's view companies should be mindful of the impression given by the presence of a representative at a practice during the provision of a service given the requirements of Clause 18.4 and its supplementary information. The Panel considered it would be helpful if there was detailed written guidance on the acceptability or otherwise of promotional calls during the period of time that the EMD service was provided and was particularly concerned that in the absence of such guidance representatives were encouraged to visit practices during the provision of the service as long as the visit was more than 24 hours either side of the service nurse working there. The Panel queried whether this, in conjunction with the direction to network at the practice, might result in a practice not fully understanding the difference between the representatives' promotional and non-promotional roles.

The Panel noted Lilly's submission about the 29 calls by representatives in relation to Lilly medicines at the 9 practices that underwent the EMD service between 2012 and 2014. The Panel was extremely concerned that no representative EMD service calls were recorded from 2012 – 2014 despite the implementation of 9 services. Lilly estimated a minimum of 3 such calls per practice. The Panel therefore queried how reliable the recorded call rates were generally. In addition it appeared that Lilly did not record telephone requests for visits which in the Panel's view was unusual. The Panel had no information about the activity of representatives from the co-sponsor of the service.

Whilst the Panel had concerns about the management of representatives, including the failure to record any service calls in the named region, it also noted its comments above about the burden of proof. The complainant's surgery had not been identified and thus it was not possible to determine precisely what had occurred there. Similarly it was not possible to determine precisely what had occurred within the local region. The Panel did not consider that the number of regional calls made during service implementation was such that representatives were 'carpet bombing' practices as alleged. In such circumstances the Panel ruled no breach of Clauses 15.2, 15.3, and 15.4 of the Code.

In relation to the EMD service, the Panel noted the complainant alleged that both at his/her practice and elsewhere the service nurse provided biased education and the service led to a disproportionate prescribing of the companies' products. The Panel noted the details of the EMD service including the training modules set out above. The Panel noted its comment above that it did not appear that any module gave disproportionate emphasis to Lilly products as alleged. The Panel noted that the supplementary information to Clause 18.4 Provision of Medical and Educational Goods and Services, stated that service providers must operate to detailed written instructions provided by the company. These should be similar to the briefing material for representatives as referred to in Clause 15.9. The Panel was concerned about the failure to provide any formal briefing on how the four training modules were to be used within GP practices. This was especially so given the modules discussed products. The Panel noted Lilly's submission that the service 'nurses were 'independent diabetes specialists who trained themselves on the module'. The Panel had no way of knowing what was said by the nurses during the training sessions.

The Panel noted its general comments and concerns about the service set out above but bore in mind that the complainant had to establish his/her case on the balance of probabilities. On balance the Panel did not consider that there was sufficient evidence to establish whether, either at the complainant's surgery or locally, the service had been offered in connection with the promotion of medicines or otherwise as an inducement contrary to Clause 18.1. No breach of that clause was ruled. Similarly the Panel did not consider that there was evidence to show that the EMD service was a disguised promotional activity; no breach of Clause 12.1 was ruled.

The Panel noted its general comments above about the service. Whilst some concerns were outlined above the Panel did not consider that there was any evidence before it to demonstrate that the service as implemented in the complainant's surgery or locally was biased towards Lilly products as alleged. Consequently the Panel ruled no breach of Clause 18.4.

Noting its rulings above the Panel ruled no breaches of Clauses 9.1 and 2.

Complaint received **23 May 2014**

Case completed **1 September 2014**

CASE AUTH/2719/6/14

VOLUNTARY ADMISSION BY AMGEN

Nominated signatories

Amgen voluntarily admitted that it had failed to notify the PMCPA and the Medicines and Healthcare Products Regulatory Agency (MHRA) of two new nominated signatories resulting in material being certified by one signatory.

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

The detailed response from Amgen is given below.

The Panel noted that the Code required that, *inter alia*, the names of those nominated as final signatories, together with their qualifications, be notified in advance to the Advertising Standards Unit, Vigilance and Risk Management of Medicines of the MHRA, and to the PMCPA. The Panel noted Amgen's submission that it had failed to notify the MHRA and PMCPA of two non-medical nominated signatories which resulted in items being certified by two signatories, only one of whom had been notified to the MHRA and PMCPA; the Panel thus ruled a breach of the Code as acknowledged by Amgen.

Consequently the materials that had been certified by the above two non-medical signatories who had not been notified in advance to the MHRA and PMCPA had not been certified in accordance with the Code and its supplementary information and the Panel ruled a breach of the Code.

Amgen Limited voluntarily admitted that it had failed to notify the PMCPA and the Medicines and Healthcare Products Regulatory Agency (MHRA) of two new nominated signatories resulting in material being certified by one nominated signatory rather than two as required by the Code.

In accordance with Paragraph 5.6 of the Constitution and Procedure the admission was treated as a complaint and the matter was taken up with Amgen.

COMPLAINT

Amgen explained that it had breached Clauses 14.1 and 14.4 due to an administrative error in dispatch of notification of two non-medical nominated signatories to the MHRA and PMCPA, resulting in promotional material being certified by one nominated signatory (a registered medical practitioner), rather than two nominated signatories as required by the Code.

Amgen stated that upon discovering the error, immediate measures were taken to ensure that no certification of any further promotional materials by the two signatories in question occurred.

Certification of fifteen current promotional items by a second nominated signatory occurred with no change of material content; seventeen promotional items no longer in use were retrospectively reviewed by a second nominated signatory without identifying any content that was considered to be non-compliant with the Code. The PMCPA and MHRA were notified of the two new nominated signatories.

Amgen stated that it took its obligations for compliance with the Code very seriously and apologised for the administrative oversight.

The Authority asked Amgen to consider this matter in relation to Clauses 14.1 and 14.4 of the Code.

RESPONSE

Amgen explained that two non-medical signatories certified material for approximately five months (January – June 2014) prior to PMCPA and MHRA notification of their names and qualifications (20 June). Amgen submitted that it reviewed its internal record of promotional materials and was confident that only thirty four promotional items were approved during that time and were impacted by the voluntary admission, a list of which was provided; two additional materials no longer in use had been identified since the initial voluntary admission. No change to the content of fifteen items in current use was required upon certification by a second nominated signatory. The content of nineteen items no longer in use was considered to be Code compliant upon retrospective review by a second nominated signatory.

Amgen submitted that the breach was discovered as a result of routine review of promotional material. A reviewer accessed promotional material certified in 2014 in order to assess consistency of content; the certificate included the name of one of the non-medical signatories in question. The reviewer was unsure whether the non-medical signatory had been added to the list of signatories notified to the PMCPA and MHRA, resulting in a review of that list. It was at that point that the administrative error in the notification of the two new signatories became apparent.

Following identification of this breach, Amgen implemented the following process to ensure documented and timely notification of signatories in accordance with Clause 14:

- Addition of suitably qualified new signatories to be agreed by an internal compliance committee (including senior leadership team members, the majority of whom were existing nominated signatories) and the decision documented in the meeting minutes.

- Compliance lead to promptly notify the PMCPA and MHRA of updated nominated signatories list and send confirmation to the compliance committee when completed.
- Following dispatch of communication, compliance lead to communicate the updated list of nominated signatories to all reviewers, approvers, and administrative support involved in the examination and certification of company material. In addition, the current list of nominated signatories would be uploaded to Amgen's intranet site accessible by all employees.

PANEL RULING

The Panel noted that Clause 14.4 required that, *inter alia*, the names of those nominated as final signatories, together with their qualifications, be notified in advance to the Advertising Standards Unit, Vigilance and Risk Management of Medicines of the MHRA and to the PMCPA. The names and qualifications of designated alternative signatories must also be given. Changes in the names of nominees must be promptly notified. The Panel noted Amgen's submission that it had failed to notify the MHRA and PMCPA of two non-medical nominated signatories which resulted in thirty four items being certified by two signatories, only one of whom had been notified to the MHRA and PMCPA as required by the Code; the Panel thus ruled a breach of Clause 14.4 as acknowledged by Amgen. Consequently the materials that had been certified by the above two non-medical signatories who had not been notified in advance to the MHRA and PMCPA had not been certified in accordance with Clause 14.1 and its supplementary information. The Panel thus ruled a breach of Clause 14.1.

Complaint received **20 June 2014**

Case completed **21 July 2014**

ANONYMOUS v GENZYME

Conduct of a Representative

An anonymous complainant referred to the conduct of a named Genzyme employee during a meeting to discuss Aubagio (teriflunomide).

Aubagio (teriflunomide) was licensed for the treatment of adults with relapsing remitting multiple sclerosis. Its summary of product characteristics stated that liver enzymes should be assessed before treatment and monitored every two weeks for the first six months.

The complainant explained that the employee met a consultant neurologist and a pharmacist to discuss Aubagio. Concerns had been raised regarding the need to accommodate the monitoring of patients on Aubagio every two weeks for the first six months. In response the employee said that another hospital unit was not going to follow the licence and was looking at monthly monitoring. The complainant stated that it was inappropriate to suggest that licensed guidelines were not followed. The complainant was concerned that the employee could be having further off-licence discussions with health professionals and possibly bringing the industry into disrepute.

The detailed response from Genzyme is given below.

The Panel noted that the parties' accounts differed. In such circumstances it was difficult to determine precisely what was said at the meeting and therefore where the truth lay. A judgement had to be made on the available evidence bearing in mind that the complainant had to establish his/her case on the balance of probabilities.

The Panel noted the complainant's allegation that the named employee had stated during a meeting with a doctor, pharmacist and a Genzyme representative that a hospital unit was looking at monthly monitoring for Aubagio patients which was outwith the product licence. The representative had raised concerns with the manager after the meeting but the manager did not recollect a discussion about off-label monitoring. Had this been raised, the manager would have reported the matter to the employee's manager. In addition, the Panel noted that the representative's record of the meeting referred to setting up central monitoring but did not indicate that anything untoward had occurred.

According to Genzyme, the named employee denied making the comments alleged and stated that in response to the doctor raising concerns about the difficulty of monitoring every two weeks, the employee stated that a number of centres were similarly concerned and referred to another hospital's shared care plan. One of the health professionals present might have mentioned monthly monitoring but the named employee could not be sure if it was mentioned at all or if it was, who might have mentioned it. The named employee was not aware of the plans for monthly monitoring but knew about the shared care plan from a medical science liaison (MSL).

According to Genzyme, the pharmacist present corroborated the named employee's position. The pharmacist thought that the doctor might have referred to monthly monitoring but disagreed with the complainant's version of the meeting. There was no evidence from the doctor before the Panel.

The Panel noted that the named employee stated that 'they discussed monitoring further'. The Panel had no information about the detail of that general discussion. The Panel considered that it was likely that if monthly monitoring had been raised by a health professional the Genzyme staff present would have responded to this concern. The Panel noted that the relevant objection handler about monitoring discussed the licensed requirements and referred the health professional to in depth hepatic safety data.

Whilst noting its concern and comments above the Panel noted that the complainant had to establish his/her case on the balance of probabilities. The complainant had been asked to comment on Genzyme's response but had stated that he/she had no additional comment to make. Given the parties' differing accounts of the meeting in question, it was impossible to determine precisely what had been said. The Panel therefore ruled no breach of the Code including Clause 2.

A complaint was received about the conduct of a named Genzyme employee during a meeting to discuss Aubagio (teriflunomide) from someone who was contactable but wanted to remain anonymous.

Aubagio (teriflunomide) was licensed for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). Elevation of liver enzymes had been observed in patients treated with Aubagio and so liver enzymes should be assessed before treatment and every two weeks during the first six months of treatment and every eight weeks thereafter (Aubagio summary of product characteristics (SPC)).

COMPLAINT

The complainant explained that a named Genzyme employee (employee 1) met a consultant neurologist and a pharmacist to discuss Aubagio. The complainant stated that various questions and concerns had been raised by the health professionals as they had yet to prescribe the medicine for their

patients. The health professionals would struggle to accommodate the monitoring of patients every two weeks for the first six months to which employee 1 replied that another unit in another named hospital was not going to follow the licence and was looking at monthly monitoring. The complainant stated that it was highly inappropriate for employee 1 to suggest that licensed guidelines were not followed. The complainant was concerned that employee 1 could be having further off-licence discusions with health professionals and possibly bringing the industry into disrepute.

When writing to Genzyme, the Authority asked it to respond in relation to Clauses 2, 3.2 and 15.2 of the Code.

RESPONSE

Genzyme submitted that it took allegations of misconduct of its employees and potential breaches of the Code very seriously.

Genzyme stated that there were four people at the meeting in question: employee 1, another Genzyme employee (employee 2), a pharmacist and the doctor. Significant efforts were made to contact and interview the doctor but unfortunately Genzyme had been unable to do so during the time allotted.

In addition Genzyme stated that it interviewed a further two Genzyme employees as a result of information which was provided during the interviews of employees 1 and 2.

Genzyme submitted that employee 1 had met the pharmacist and doctor prior to the call in question and was invited to meet to talk about Aubagio. Employee 2 was new to the business and employee 1 agreed to introduce him/her at the meeting.

Genzyme provided a copy of the Aubagio Risk Management Plan which discussed patient monitoring in the first six months of treatment, along with the certificate of approval. No briefing materials were used during the meeting.

Genzyme provided a copy of the Aubagio SPC and submitted that there were no briefing materials which had been sent to the field force or commissioning specialists about the named hospital's alleged proposal not to follow Aubagio's licence with regard to patient monitoring. Employee 1's evidence was that he/she was not aware that this unit had any plan to go off-licence. Genzyme stated that employee 1 had passed the representatives' examination and employee 2's entry on the customer relationship management (CRM) database for the meeting in question was provided.

Genzyme submitted that it had obtained three accounts of the meeting. Employee 2's account concurred with the anonymous complaint. Genzyme submitted that there was strong concordance between the full and detailed accounts of the meeting provided by employee 1 and the pharmacist; both agreed that employee 1 did not state that the other hospital was not going to follow the licence as alleged.

In addition, employee 2 stated that he/she had told the manager of the concern on the day of the meeting and Genzyme therefore interviewed the manager as part of the investigation. While the manager confirmed that employee 2 had raised various concerns about the meeting his/her recollection was that those concerns were about employee 1's poor preparation for the meeting and weakness in objection handling. The manager could not recall any mention of advice or promotion that deviated from the SPC and if told that employee 1 had dealt inappropriately with an 'off-label' question his/her manager would have been contacted as that would have been a more serious issue requiring corrective action.

Employee 1's account

Genzyme submitted that employee 1 had been invited to meet the pharmacist and doctor to talk about Aubagio. Employee 2 was new and was invited to be introduced. During the meeting formulary was discussed and the doctor raised concerns about the difficulty of monitoring patients once every two weeks but employee 1 did not say that the other hospital was looking at monthly monitoring for patients.

Employee 1 stated that a number of centres had raised this concern and the health professionals might have stated that they had heard that the other hospital might be monitoring monthly. Employee 1 stated that he/she had not been aware of this; the licence required monitoring once every two weeks in the first six months of treatment and he/she understood that the other hospital was planning to put a shared care programme in place with GPs to manage the monitoring requirements in the licence. Employee 1 submitted that they discussed monitoring further and he/she suggested that a medical science liaison (MSL) should arrange to discuss the matter in further detail.

Genzyme asked employee 1 how he/she knew what the other hospital was planning to do with regard to monitoring and was told that an MSL colleague had provided the information.

Employee 1 stated that he/she had a difficult relationship with employee 2; employee 1 had raised a grievance against employee 2 which had been upheld ten days before the complaint was received by the PMCPA and he/she considered that that was the reason for the complaint.

Interview with MSL colleague

Genzyme interviewed the MSL who had told employee 1 about the other hospital's plans and asked about these plans without giving the background to the question. The MSL corroborated employee 1's account stating that a named doctor had been quite vocal (including at national conferences) about his thoughts that the science did

not merit monitoring patients once every two weeks in the first six months but that the hospital had nonetheless accepted the recommendations in the SPC. The MSL was very clear that the other hospital planned to enter into a shared care arrangement, initially on a case-by-case basis, with GPs to carry out twice monthly monitoring and had a number of patients with whom such monitoring arrangements had been agreed with GPs.

Employee 2's account

Genzyme interviewed employee 2 who stated that employee 1 had said that the hospital was not going to follow the licence and was looking at monitoring monthly for patients. Employee 2 stated that the doctor had stopped employee 1 as it was not in accordance with the licence and he/she did not want to talk about anything off-label. Employee 2 stated that he/she felt embarrassed and challenged employee 1 about the statement after the meeting. Employee 2 also stated that he/she had informed the line manager in a telephone call after the meeting that employee 1 had made such a statement about monitoring and showed Genzyme an (undated) email on the subject that had been saved but never sent. Employee 2 submitted unprompted that he/she had a difficult relationship with employee 1.

Interview with employee 2's line manager

Genzyme submitted that the line manager stated that he/she had no recollection of employee 2 telling him/her that employee 1 had suggested that the hospital was not going to follow the licence for monitoring of Aubagio. The line manager recalled that employee 2 had called after the meeting, unhappy with the way it had gone. The line manager also recalled that on another occasion employee 2 had mentioned that another health professional at a different centre had mentioned monthly monitoring and on this occasion immediately informed the health professional that the requirement in the licence was to monitor once every two weeks for the first six months. This was to illustrate and provide evidence for the line manager's belief that if employee 1 had promoted off-label he/she would have expected employee 2 to intervene and corrected it and he/she would have reported this to employee 1's line manager.

Account of the meeting from the pharmacist

Genzyme submitted that the pharmacist stated that he/she recalled the meeting because the relationship between the two Genzyme employees seemed strained and he/she wondered if there was difficultly between them. The pharmacist stated that he/she vaguely remembered the conversation about the other hospital; the two doctors in the two hospitals knew each other and the pharmacist thought it was the doctor in the meeting who had said that the other doctor might be going to monitor patients monthly; employee 1 did not say that. When asked whether the doctor in the meeting had stopped employee 1 as he/she did not want to talk about monitoring off-label, the pharmacist stated that it did not sound like something that doctor would say.

Genzyme concluded that given the above, the weight of evidence suggested that the impropriety alleged in the anonymous complaint did not take place.

In response to a request for an explanation regarding what employee 1 knew of the plan to go off-licence with regard to monitoring and what was said about it during the meeting, Genzyme explained that the plan referred to by employee 1 and the MSL was not the same as the plan referred to by employee 2. The plan meant different things to different people. The shared care plan was not off-licence or inappropriate. The evidence suggested that employee 1 believed the other hospital was planning to implement a program of shared care with GPs to monitor every 2 weeks in line with the SPC. It was what employee 1 said he/she believed and the MSL independently confirmed this was what he/she discussed with employee 1.

Employee 1 recounted that when the pharmacist and doctor brought up the fact that they thought fortnightly monitoring presented a challenge, he/she had empathised, confirming that a number of centres felt the same way, but only spoke about shared care as a possible route to a solution. This would not be off-licence. When asked if a monthly monitoring interval was discussed, employee 1 replied to Genzyme that one of the health professionals at the meeting might have mentioned it, but could not remember for sure if it was mentioned at all or, if it was mentioned, who might have mentioned it. Again, employee 1 did not appear to say or do anything inappropriate by this account. Additionally, employee 1's evidence was supported by the pharmacist's recollection who recalled that the doctor spoke a bit about the other hospital, but could not remember for sure if he/she had mentioned monthly monitoring. The pharmacist was very confident however that employee 1 had not mentioned it and no one had taken from the meeting that monthly monitoring might be an option.

It was the MSL's evidence that the other hospital never had a plan to monitor monthly. This was backed up anecdotally by a senior sales manager who was surprised about the nature of the complaint because all his/her conversations with the other hospital had been about monitoring fortnightly in line with the SPC.

Genzyme submitted that the monthly plan would be off-licence and inappropriate. Employee 1's evidence, supported by the pharmacist, was that at no point during the description of the other hospital's plans or what he/she said about them had he/she referred to an inappropriate/off-licence monthly plan.

In response to a request for a copy of employee 1's entry on the customer relationship management (CRM) database for the meeting, Genzyme submitted that there was no such entry. It was Genzyme's policy that if two colleagues were in the same meeting only one of them entered it in the CRM. This was to prevent double counting of visits and misunderstanding its coverage and frequency.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant had no additional comments on Genzyme's response.

Genzyme subsequently, at the Panel's request, provided a copy of the representatives' briefing material for Aubagio.

PANEL RULING

The Panel noted that the parties' accounts differed. In such circumstances it was difficult to determine precisely what was said at the meeting and therefore where the truth lay. A judgement had to be made on the available evidence bearing in mind that the complainant had to establish his/her case on the balance of probabilities.

The Panel noted that Section 4.4 of the SPC, Special warnings and precautions for use, stated that during treatment blood pressure, alanine aminotransferase (ALT/SGPT), and complete blood cell counts based on signs and symptoms (eg infections) during treatment should be monitored. Liver enzymes should be assessed before initiation of therapy and every two weeks during the first six months of treatment and every eight weeks thereafter or as indicated by clinical signs and symptoms, examples were given. In addition, for ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. The briefing document on Aubagio's risk management plan referred to the monitoring requirements in the SPC. The Panel noted that in some areas shared care plans existed where monitoring responsibilities in line with the marketing authorisation were shared with primary care.

The Panel noted the complainant's allegation that employee 1 had stated during a meeting with a doctor, pharmacist and employee 2 that a unit in another hospital was looking at monthly monitoring for patients which was outwith the product licence. According to Genzyme, employee 2's account supported the complaint. Employee 2 had raised concerns with his/her manager after the meeting. The manager, however, whilst noting that concerns about the meeting had been raised did not recollect mention of a discussion about off-label monitoring. Had this been raised the manager was sure that he/she would have reported the matter to employee 1's manager. In addition, the Panel noted that employee 2's CRM entry referred to setting up central monitoring but did not indicate that anything untoward had occurred.

According to Genzyme, employee 1 denied making the comments alleged and stated that the doctor present had raised concerns about the difficulty of monitoring every 2 weeks. In response, employee 1 had stated that a number of centres had raised this concern and referred to another hospital's shared care plan to manage the licensed monitoring requirements. One of the health professionals present might have mentioned monthly monitoring but he/she could not be sure if it was mentioned at all, or if it was mentioned, who might have mentioned it. Employee 1's position was that he/she was not aware of the plans for monthly monitoring but he/she knew about the shared care plan from an MSL. According to Genzyme, the MSL in question corroborated employee 1's view and was clear that the shared care arrangement monitored within licence. However, the MSL was also clear that a named doctor from the other hospital had publicly stated that, in his/her view, the science did not merit monitoring patients every two weeks for the first six months of treatment but nonetheless the other hospital would comply with the licensed requirements. It was unclear whether this latter information had been given to employee 1 by the MSL.

According to Genzyme, the pharmacist present corroborated employee 1's position. The pharmacist thought that the doctor present might have referred to monthly monitoring but disagreed with the complainant's version of the meeting. There was no evidence from the doctor before the Panel.

The Panel noted that employee 1 stated that 'they discussed monitoring further'. The Panel had no information about the detail of that general discussion. The Panel considered that given the company's adoption of the needs based selling model which required representatives to actively seek out concerns and objections it was likely that if a monthly monitoring model had been raised by a health professional the Genzyme staff present would have responded to this concern. The Panel noted that the objection handling section of the campaign briefing document (AUBA-UK-12/13-4737) in response to a concern about monitoring, discussed the licensed requirements and referred the health professional to in depth hepatic safety data.

The Panel noted that the complainant had to establish his/her case on the balance of probabilities. The complainant had been asked to comment on Genzyme's response but had stated that he/she had no additional comment to make. Given the parties' differing accounts of the meeting in question, it was impossible to determine precisely what had been said. The Panel therefore ruled no breach of Clauses 2, 3.2 and 15.2 of the Code.

Complaint received **19 June 2014**

Case completed **23 October 2014**

CASE AUTH/2722/7/14

ANONYMOUS EX-EMPLOYEE v ORION

Respiratory reviews

An anonymous, non-contactable, complainant who stated that he/she was an ex-employee of Orion Pharma UK was concerned about respiratory reviews being carried out in GP surgeries on Orion's behalf. Orion marketed three Easyhalers for the treatment of asthma (Easyhalers salbutamol, beclometasone and budesonide) and one Easyhaler for use in asthma or chronic obstructive pulmonary disease (COPD) (Easyhaler formoterol).

The complainant explained that Orion payed an external company to conduct the reviews to alter GPs' prescribing habits and although the reviews were independent, Orion knew that a cost based review would mean patients were switched to an Orion Easyhaler.

The complainant stated that at the start of the 2014 conference, representatives were told that signing up these reviews was critical for Orion's success that year and since then representatives had been under increasing pressure to sign up GPs. The complainant questioned how that could be if the reviews were non-promotional.

The detailed response from Orion is given below.

The Panel noted that the complainant was anonymous and non-contactable. As with all complaints the matter would be judged on the evidence provided by the parties; the complainant bore the burden of proof. The complainant in this case, who could not be contacted for further information, alleged that Orion had paid a third party to conduct respiratory review services which in effect served to switch patients to Orion medicines.

The Panel first examined how the representatives were briefed about the review service.

The Panel noted potential for confusion given that the same abbreviation was used to refer to the company conducting the reviews and a type of treatment. The Panel queried whether some representatives might assume that they were being encouraged to sign up GPs for the respiratory review service because it was the way to achieve the level of Easyhaler sales as set out on slides used at the January and May 2014 national sales meetings. The Panel further noted that a presentation given by a representative at the May conference referred to cost efficiencies and the Panel considered that the aim of this presentation was to discuss strategies which had been successful in getting GPs to sign up for the service.

It was clear to the Panel that Orion was promoting and the representatives were detailing, at least in part, Easyhalers as a less expensive prescribing choice that the prescriber could consider switching his/her patients to. A slide set entitled 'COPD and Asthma background', which appeared to be aimed at representatives, included a slide which referred to the aims and objectives of the respiratory review service and stated 'Clinical and Financial benefit without burdening practice Resources'. Notes accompanying the slide stated that if during a promotional visit a change in medication to an Orion product was agreed, the respiratory review service could not be offered as this would be a means of the company making sure that the change would be made. It was not stated what was to happen if a change to Orion's products was agreed in the separate non-promotional meeting that a representative might arrange to detail the service.

The Panel was extremely concerned about the impression that the leavepieces, which encouraged switching patients to Easyhaler and other material which detailed cost savings with Easyhaler, would give if they were also left with the leavepiece about the respiratory review service. The Panel noted Orion's submission that the respiratory review programme was initiated, at least in part, in response to the upward-spiralling spend on respiratory medicines. The Panel considered that given the content and tone of some of the promotional material, it was not unreasonable to think that some GPs might be persuaded to use the service to switch patients from their current inhalers to the generally less expensive Easyhalers. In this regard, the Panel noted that although practices could agree their own bespoke review and thus identify the patient cohorts they wanted to be included, the second patient cohort referred to in the template review protocol provided was 'Patients receiving non practice preferred inhaled preparations to be clinically assessed to highlight opportunities for improved management & change to practice preferred device/preparation to improve budgetary efficiency'. The Panel queried whether this cohort of patients would be clinically reviewed as it appeared that they might, for no clinical reason, be switched to alternative therapies that were either 'practice preferred' or which improved budgetary efficiency. The Panel noted Orion's submission that representatives delivered this document to surgeries in a non-promotional call to show what the service consisted of and explain the nature of the service before the practice signed up to the service. The Panel further noted that the letter template for patients in cohort 2 appeared to show that such patients could have their inhalers changed without a face-to-face consultation with a health professional; the patient was advised that if they would like to discuss the changes that had been made, which could include a new device and/or dosage regimen, then they could see the practice nurse or direct any queries to their community pharmacist who would be able to demonstrate the new device. The Panel queried whether the arrangements for patients

in cohort 2 were acceptable given how important compliance and the correct use of devices was to the control of asthma.

The Panel noted Orion's campaign promoted a switch to Easyhaler devices on the basis of cost. There must be a clear, visible demarcation between any promotional activity and the offer and implementation of the therapeutic review otherwise the review could be seen as a switching service contrary to the Code. The Panel noted its comments above about the representatives' briefing. In the Panel's view, some representatives would have been left with the unacceptable impression that the service was to be used as a vehicle to increase sales. The Panel also noted the unacceptable impression given by the Easyhaler leavepieces when left at a practice with the service leavepiece and the second patient cohort referred to in the protocol. In the Panel's view, and on the balance of probabilities, the combined effect of the above was that prescribers were more likely to switch patients to Easyhaler devices; the Panel ruled breaches of the Code. The Panel considered that to provide representatives with materials which referred to switching and then ask them to leave material which introduced a therapy review programme meant that high standards had not be maintained. A further breach was ruled. The Panel noted that the complainant had made no specific allegation with regard to the conduct of any representative. In the Panel's view, by using the materials provided and introducing prescribers to the service, representatives had complied with their briefings and in that regard had not failed to maintain high standards. The Panel ruled no breach of the Code.

The Panel acknowledged the clinical value of a therapy review service for asthma patients and although it had particular concerns about cohort 2 (if the GP decided to include such a cohort in the review), it considered that on balance the respiratory review service had not been 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 who stated that he/she was an ex-employee of Orion Pharma UK Ltd was concerned about respiratory reviews being carried out in GP surgeries on Orion's behalf. Orion marketed three Easyhalers for the treatment of asthma (Easyhalers salbutamol, beclometasone and budesonide) and one Easyhaler for use in asthma or chronic obstructive pulmonary disease (COPD) (Easyhaler formoterol).

COMPLAINT

The complainant explained that Orion payed an external company to conduct respiratory reviews in GP surgeries to alter their prescribing habits. The complainant stated that although the reviews were independent, Orion knew that a cost based review would mean patients were switched to an Orion Easyhaler.

The complainant stated that at the start of the 2014 conference, representatives were told that signing up these reviews was critical for Orion's success that year and since then representatives had been under increasing pressure to sign up GPs to undergo review. The complainant questioned how that could be if the reviews were non-promotional.

The complainant stated that he/she had been told that at a recent conference, a representative [from a named territory] gave a presentation which compared how many reviews he/she had arranged and the rise in sales; representatives in attendance were told to speak to the presenter to find out how he/she had done it.

When writing to Orion, the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 18.1 and 18.4 of the Code.

RESPONSE

Orion submitted that it was a relatively small team that prided itself on its open approach to communication. Its two regional sales managers managed eighteen respiratory representatives; a further five representatives worked in other therapeutic areas. Orion provided details of its respiratory range of products: Easyhaler Salbutamol Sulphate, Easyhaler Beclometasone, Easyhaler Budesonide, Easyhaler Formoterol.

Orion liked to think that team members could bring their concerns to the management's attention informally, but it also had a clear public interest disclosure or 'whistle-blowing' policy in the UK and so it was very disappointed that its former employee felt unable to raise his/her serious concerns through one of these mechanisms whilst still employed. Orion submitted that it took such matters extremely seriously and as a consequence, launched an internal review and investigation. Senior members of the medical department interviewed key individuals involved in providing the respiratory review service and reviewed all current documents and associated working practices.

The respiratory review service

Orion funded an independent third party service provider to conduct respiratory reviews as a service to medicine; such reviews were conducted to improve the management of asthma and COPD to the benefit of patients and the NHS, and not to alter GPs' prescribing habits as alleged. The programme of reviews was initiated in 2009 to improve the quality of asthma treatment across local health economies. To date over two hundred reviews had been carried out at practices. The programme was initiated in response to the upward-spiralling spend on respiratory medicines and high levels of hospital admissions for respiratory problems. Orion submitted that enabling asthma to be more efficiently managed in primary care, benefitted patients and the NHS.

Orion submitted that the respiratory reviews were essentially clinical audits. They were conducted with all reasonable skill and care and complied with relevant established current professional standards and the code of ethics set down by the General

Pharmaceutical Council (GPhC). The aims and objectives of the audits were to:

- Facilitate active case finding of patients with undiagnosed COPD in order to improve early identification and management and thus disease outcomes and the patient's quality of life.

- Identify patients at risk of asthma or COPD exacerbations. Risk stratification of patients allowed the practice to prioritise work streams within COPD and asthma management. Improved management of high risk patients supported a reduction in respiratory referrals and overall disease morbidity and mortality.

- Identify and realise prescribing efficiencies to minimise the budgetary impact of earlier pharmacological interventions in high exacerbation risk and the pharmacological management of newly diagnosed patient groups.

Orion stated that the service provider operated entirely independently of Orion in accordance with the clinical requirements of the practice and the needs of each patient. Orion was not able to influence the use of any specific medicine or product during this process. Use of the respiratory review service was not connected with the prescription of any Orion product. The protocol used directed the cycle of the clinical audit and the therapy review reflected many of the principles laid out in the best practice guidance for clinical audit by the NHS using risk stratification tools to profile patients whilst tackling medicines management objectives relating to therapy. Each practice that used the service agreed its own bespoke review specification and objectives with the service provider pharmacist. Clinical assessment of patients was in accordance with the British Thoracic Society (BTS) Guidelines, local formularies and practice review specification; patients' medical records were reviewed individually. The protocol included options for: case finding for COPD patients; identification of sub-optimally controlled asthma patients; 'stepping down' of treatment for well controlled asthma patients; rationalisation of prescribed inhaler preparations and identification of any other patient cohorts that the practice chose. The service provider pharmacist prepared recommendations within this framework for the doctor responsible for prescribing decisions. All prescribing decisions remained solely with the physician.

Orion noted that the complainant alleged that the company knew that a cost based review would mean that patients would be switched to an Easyhaler. Orion submitted that as was clear from the protocol, the review service was based on optimising patient treatment and there was no specific option for a 'cost based review'. Any changes to treatment were made on the basis of reviewing the patients' medical records and the prescriber decided which treatment to use.

In line with the requirements of the Code, representatives were instructed that the provision of the service was non-promotional and so it must not be discussed during a promotional appointment. Representatives were advised that in order to comply with this requirement they must not carry out promotional and non-promotional activities at the same visit, and that the service could not be provided to a practice that had stated its intention to change patients to Orion products as this would, effectively, mean Orion had paid for prescriptions. Representatives could introduce the service by means of a brief description and/or delivering materials but could not instigate a detailed discussion about the service in the same call in which they promoted products.

Orion submitted that when representatives joined the company their initial training included training on the respiratory review service by one of the marketing team. A copy of the presentation was provided. Regional sales managers continually reviewed representatives' training needs during field visits and provided coaching or arranged additional training as necessary.

Briefings at the January 2014 and May 2014 sales conferences

Orion submitted that it was careful to ensure that any discussion of the respiratory review service at sales meetings (held in January, May and September each year) was in a separate section of the agenda and not directly linked to any sales presentations. For example, discussions would be separated by tea breaks and lunch from the sales sections.

Orion noted that the complainant alleged that at the start of the 2014 conference the representatives were told that signing up of these reviews was critical for the success of Orion that year. Orion acknowledged that the respiratory review service was discussed at the January 2014 sales conference but it was never described as being critical for Orion's success.

The session about the respiratory review service was a minor section of the presentation which took the form of a reminder that a new service leavepiece was available. The sales team was advised that the leavepiece could be left with customers at the end of a promotional meeting but that details of the service could not be discussed with customers at that time. Less than 15 minutes was spent on this item during a two day meeting. Copies of the presentation from the January sales meeting, the leavepiece and associated briefing material were provided.

Orion submitted that the findings of its internal enquiry based on interviews with representatives and managers showed that at the January sales meeting the Easyhaler brand was described as important, vital and critical to the company; however, none of these words were used to describe the use or importance of the respiratory review service to Orion. Those interviewed described the value of the service to Orion as 'not vital to Orion but important' and more generally in terms of value to the customer, for example 'offering value to the customer and a helpful service'.

Orion noted that the complainant stated that 'Since that conference representatives have been under increasing pressure to sign up GPs for reviews'.

Orion submitted that the company had never asked representatives to increase the number of general practice 'sign-ups' for this service. Representatives were not measured or targeted on respiratory reviews and were not bonused on activity in relation to them.

Orion noted that the complainant went on to state 'I was told that at the recent conference a representative from [a named territory] gave a presentation on the comparisons of how many reviews he/she had signed up and the rise in sales. Representatives at the presentation were told to speak with the presenter to find out how he/she did it.' Orion submitted that this did not take place.

Orion submitted that at the most recent sales meeting (May 2014), there were four ninety minute workshop sessions on respiratory topics. Topics discussed were 'Implementing local guidelines/ formularies', 'Selling the Easyhaler Steroids - Use of materials', the 'My Well-being' application for smartphones and a session on the introduction of the respiratory review service to customers. Each session began with a short informal introduction by a member of the sales team followed by unscripted round table discussions amongst the representatives. One of these workshops was introduced by the representative responsible for the territory referred to in the complaint and took place during the 'Introduction of the respiratory review service to customers' session. This session was separate from the sales content of the meeting and the representative prepared some slides to act as an aide memoire and these were shown to the group. The session explained how a local clinical commissioning group (CCG) used the respiratory review service to implement its respiratory guidelines (a copy of the presentation was provided). In contradiction to the complainant's assertion, the presentation did not show the number of reviews that had taken place, nor did it provide any sales data.

The representative was interviewed as part of the investigation and confirmed that the aim of the session was to describe the benefit of working in partnerships with the CCG during the implementation of its local guidelines and that 'sales' were not mentioned during the session and the sales team was not instructed to talk to the presenter to find out more information on increasing sales using this mechanism. All questions and discussions during the workshop were on the subject of working with CCGs to implement guidelines.

Actions

Orion stated that in response to this complaint, its internal review and investigation had resulted in a number of immediate actions:

- The nature and significance of the complaint has been communicated to all staff including the sales team, and representatives had been reminded of correct procedures associated with the use of the respiratory review service, the importance of complying with the Code and the procedures for raising concerns.
- The medical team would conduct a further, detailed review of all processes and materials connected to the respiratory review service and report its findings together with an action plan for any remedial activities that might be required.

Orion submitted that as a result of its investigations it was disappointed to report that the presentations at the May sales meeting were not certified before use; the failure to comply with company procedures was due to a prolonged period of serious illness during the preparation period for the sales meeting and a lack of appropriate delegation of tasks. The respiratory review training presentation had not been certified. This appeared to have been due to a lack of understanding of requirements. A programme to retrain and validate the sales managers and marketing team on company procedures for the review and approval of materials had been initiated.

Conclusions

Orion submitted that in its view, the complainant's concerns could and should have been dealt with by using the company complaints, whistle-blowing or grievance procedure. From its investigations Orion was confident that the respiratory review service was not used as a promotional tool or linked in any way to the promotion or prescription of Orion medicines, and that the independent service was of value to the NHS. It was not supplied or offered in connection with promotion or as an inducement to prescribe and was therefore not in breach of Clause 18.1. The service provided a genuine therapeutic review, which aimed to optimise patient treatment through consideration of a range of relevant treatment choices and was consistent with the requirements of Clause 18.4.

Consequently Orion did not believe that either the respiratory review service itself, or the way it was offered to customers were such as to bring discredit upon or reduce confidence in the industry and that a breach of Clause 2 could be ruled. However, the use of uncertified internal training materials identified during the investigation of this matter meant that Orion had failed to maintain high standards and on that basis it acknowledged a breach of Clause 9.1.

Orion submitted that its representatives offered the respiratory review service to customers as a non-promotional activity and it had no influence over any outcomes of the review. Orion submitted that its enquiry had failed to elicit any information that suggested its representatives had not maintained a high standard of ethical conduct or complied with all relevant requirements of the Code and there had been no breach of Clause 15.2.

In response to a request for more information, Orion provided copies of all current materials associated with the respiratory review service. Orion stated that as the service provider worked independently of Orion, Orion did not provide any briefing documents to the service provider pharmacists.

The audience for each item was as follows:

Item	Audience
Respiratory Review Protocol	GPs, CCG stakeholders, practice nurses, respiratory nurses, respiratory physicians
Letter Template for cohort 1 – COPD patients with FEV1 >50% without long acting beta agonist (LABA) or long acting muscarinic antagonist (LAMA) therapy	Patients
Letter template for cohort 2 – Patients receiving inhaled preparations outside of the practice preference -including LABA and LAMA	Patients
Cohort 3 – Patients at BTS step 3 (lowest dose) to be considered for step down to having a separate short-acting beta agonist (SABA) and inhaled corticosteroid	Patients
Briefing document for respiratory prescribing review leavepiece	Representatives
Adherence to prescribed medication letter	Patients
Change of therapy letter	Patients
Change of preparation letter	Patients
Invite to routine asthma/COPD review	Patients
Respiratory prescribing review introductory leavepiece	GPs

Copies of all current Easyhaler promotional material were provided.

Orion submitted that the representatives delivered the template Respiratory Review Protocol (reference EAS4044(1)) to surgeries in a non-promotional call to show the GP/practice what the service consisted of and explain the nature of the service and what the service provider pharmacist would do, before the practice signed up to the service. The service provider pharmacist was responsible for completion of the protocol in conjunction with the GP/practice during the respiratory review.

In response to a further request for more information, Orion reiterated that the Respiratory Review Protocol (EAS4044(1)) was the document that the service provider pharmacist completed with the lead GP and practice manager. All work undertaken by the service provider pharmacist during the review was entirely driven by and within the scope of this pivotal certified document only after the document had been signed by the lead GP and practice manager. The work of the service provider pharmacist was therefore controlled and directed by the protocol document, adherence to which was monitored by the practice signatories, service provider regional managers and regional trainers. The service provider managers and trainers were senior pharmacists who undertook regular field visits with the service provider pharmacist to assess and support them in all aspects of their work.

Orion stated that each service provider pharmacist had an average of seven years' post-graduate clinical experience. Each pharmacist underwent a six-month training period, during which they received a minimum of thirty training days via a mix of classroom, on the job training/shadowing of colleagues, and in-service training from the service provider regional managers and regional trainers. Only on successful completion of this training programme were the service provider pharmacists signed out of their probationary period, beyond which they continued to be regularly field visited by regional manager and regional trainers. A copy of the service provider internal field visit proforma, which was completed as a training record during these visits was provided. All training was documented in line with GPhC guidance. The clinical skills of the service provider pharmacist combined with training and in-service support given by the service provider gave each pharmacist the technical skills to deliver the respiratory review service. The Respiratory Review Protocol (EAS4044(1)), signed by the lead GP and practice manager, gave the service provider pharmacist the specific scope, direction and permissions required to deliver the review.

Orion explained that as part of the six-month induction programme, the service provider trained its pharmacists on the Code. The company was assured that the service provider pharmacists were aware of the requirements of the Code in relation to the wide range of services that the service provider delivered on behalf of a wide range of clients. The latest version of the Code was available to all service provider pharmacists at all times, with any significant changes briefed out at internal meetings. The service provider regional managers and regional trainers regularly assessed their teams of pharmacists for awareness of and compliance with the Code when delivering services that involved Orion. This was monitored during routine field visits and all training was documented.

Orion provided a copy of the agreement between it and the service provider which it noted stated payment and procedural terms and conditions, and the details of service delivery referred to the pivotal Respiratory Review Protocol document (EAS4044(1)).

With regard to a further request for more information, Orion provided a copy of the Pharmacist Briefing Document that applied to the service provider pharmacists. This was a service provider document used by that organisation to brief its staff.

Orion confirmed that a written signature of permission was captured for each and every patient in order to permit the service provider pharmacist to implement a treatment change.

The service provider pharmacist presented information to the GP on a data capture sheet which included a free text section. This included the result of a comprehensive clinical assessment and collation of data in order to ensure an informed treatment decision (as per the protocol).

The briefing document confirmed that service provider pharmacists must get the GP's signature consenting to any changes he/she wished the service provider pharmacist to make. Page 10 of the protocol indicated that changes were agreed on an individual basis via written authorisation. This authorization was the GP's signature; with a tick added once any change was implemented.

Section 3-6 of the protocol allowed the service provider pharmacist to take direction in order to follow the prescriber's specification regarding preferred treatment pathways. This direction was used to support the rationale for treatment change but did not preclude, but rather supported the individual decision taken for each patient by the patient's GP. All changes of treatment were documented in each patient's notes.

With regard to the service contract, the service provider issued a general service contract that was used when providing services to a range of commissioning organisations such as the NHS, research organisations and the pharmaceutical industry. Not all of the stipulations within the contract were relevant to Orion, for example the 'initial shadowing and supervision of [service provider] staff' would not be appropriate in the service at issue, but would be appropriate to an NHS organisation. Therefore, as stated above, because the service provider worked independently of Orion, Orion did not provide any briefing documents to the service provider pharmacists.

Orion stated that the service contract was dated May 2014 because this was when the agreement was last updated. This agreement superseded an earlier contract dated February 2011.

In response to a final request for more information, Orion stated that two sets of slides used at the sales meeting used the same abbreviation to refer to two different things. The phrase used by the representative, 'Utilise Techs effectively', referred to collaboration with pharmacy technicians in the local medicines management team. The representative liaised with the pharmacy technicians to ensure that GP practices were aware of local services that were provided by the medicines management team; which in turn would help facilitate GP practices 'signing-up' for such services. No notes were prepared by the representative for this presentation.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. As with all complaints the matter would be judged on the evidence provided by the parties; the complainant bore the burden of proof. The complainant in this case, who could not be contacted for further information, had alleged that Orion had paid a third party, to conduct respiratory review services which in effect served to switch patients to Orion medicines. The complainant further alleged that representatives were under increasing pressure to get GPs to sign up for the service.

The Panel first examined how the representatives were briefed about the respiratory review service and noted that in some materials an abbreviation referred to the name of the service provider whilst in others the same abbreviation referred to a type of treatment. This was not helpful. The Panel noted that at the national sales meetings held in January and May 2014, a slide headed 'Easyhaler Strategy' had been used at least twice at each meeting. The slide stated 'Achieve £6M in sales by growing [abbreviation] and maintaining Formoterol sales growth'. Orion explained that in this presentation the abbreviation stood for a type of treatment but the Panel queried whether some representatives might assume it related to the service provider and that they were being encouraged to sign up GPs for the respiratory review service because it was the way to achieve the £6M Easyhaler sales. The Panel further noted that a presentation given by a representative at the May conference referred to cost efficiencies and the first two bullet points on slide 3 stated 'Deliver cost savings in line with protocol' and 'Utilise [abbreviation] – CCG, Public Health, Networks' respectively. Orion explained that in this presentation the abbreviation related to the service provider. The second bullet point on slide 3 was also used as the first bullet point on slide 4. Slide 5 referred to the use of technicians to 'endorse sign up'. The Panel considered that the aim of this presentation was to discuss strategies which had been successful in getting GPs to sign up for the service.

The Panel noted that representatives were provided with leavepieces for the Easyhaler and for the respiratory review service. A one page, A4, Easyhaler leavepiece (ref EAS4354, prepared May 2014) was headed 'Real Life Research in Asthma' and detailed a study by Price *et al* (2014); it was sub-headed, 'Switching real-life asthma patients from other types of inhaler to the Easyhaler for the administration of inhaled corticosteroids (ICS); an historical, matched cohort study'. In the Panel's view the leavepiece encouraged recipients to consider switching their patients currently on other inhaled corticosteroids to an Easyhaler corticosteroid device. The prescribing information for Easyhaler beclometasone was on the reverse. Price *et al* was

also used as the basis for an advertisement in a conference brochure (ref EAS4349, prepared July 2014) with similar text to that in the leavepiece just described. A cost comparison guidance sheet (ref EAS4036B(5), prepared May 2014) detailed the cost savings that could be made by prescribing Easyhaler devices rather than other inhalers and another leavepiece (ref EAS4042b(1)) was sub-headed 'Easyhaler Formoterol – has the lowest 28 days treatment cost of all inhaled LABAs or LAMAs'. The representatives were also provided with a Cost Comparison Excel Tool (ref EAS3502e(3)); the accompanying covering letter stated 'Using the selection of inhalers that you made and changing them to Easyhaler, the estimated annual saving would be as follows:'. In the Panel's view it was clear that Orion was promoting and the representatives were detailing, at least in part, Easyhalers as a less expensive prescribing choice that the prescriber could consider switching his/her patients to. In that regard, it noted that in a slide set entitled 'COPD and Asthma background', which appeared to be aimed at representatives, slide 6 referred to the aims and objectives of the respiratory review service and stated 'Clinical and Financial benefit without burdening practice Resources'. Notes accompanying the slide stated that if during a promotional visit a change in medication to an Orion product was agreed, the respiratory review service could not be offered as this would be a means of the company making sure that the change would be made. It was not stated what was to happen if a change to Orion's products was agreed in the separate non-promotional meeting that a representative might arrange to detail the service.

With regard to switching the Panel noted that the supplementary information to Clause 18.4 of the Code, Switch and Therapy Review Programmes, stated that it would be acceptable for a company to promote a simple switch from one product to another but not to assist a health professional in implementing that switch even if assistance was by means of a third party such as a sponsored nurse or similar. Such arrangements would be seen as companies in effect paying for prescriptions which was unacceptable. In that regard the Panel was extremely concerned about the impression that the leavepieces described above would give if they were also left with the leavepiece about the respiratory review service (ref RESP4270, prepared December 2013) which stated that one of the outcomes of the service would be to 'Achieve best value from treatment' and that the practice report could include 'Identification of prescribing efficiencies in order to minimise the budgetary impact of earlier and/or more appropriate treatment interventions across the wider respiratory patient group'. The Panel noted that in the briefing document for the leavepiece, representatives were instructed that a detailed discussion of the respiratory review service should be conducted in a separate appointment following on from, and completely separate to, Easyhaler promotional activity. The Panel noted Orion's submission that the respiratory review programme was initiated, at least in part, in response to the upward-spiralling spend on respiratory medicines.

The Panel considered that given the content and tone of some of the promotional material, it was not unreasonable to think that some GPs might be persuaded to use the service to switch patients from their current inhalers to the generally less expensive Easyhalers. In this regard, the Panel noted that although practices could agree their own bespoke review and thus identify the patient cohorts they wanted to be included, the second patient cohort referred to in the template review protocol provided (ref EAS4044(1)) was 'Patients receiving non practice preferred inhaled preparations to be clinically assessed to highlight opportunities for improved management & change to practice preferred device/preparation to improve budgetary efficiency'. The Panel queried whether this cohort of patients would be clinically reviewed as it appeared that they might, for no clinical reason, be switched to alternative therapies that were either 'practice preferred' or which improved budgetary efficiency. The Panel noted Orion's submission that representatives delivered this document to surgeries in a non-promotional call to show the GP/practice what the service consisted of and explain the nature of the service and what the service provider pharmacist would do, before the practice signed up to the service. The Panel further noted that the letter template for patients in cohort 2 appeared to show that such patients could have their inhalers changed without a face-to-face consultation with a health professional; the patient was advised that if they would like to discuss the changes that had been made, which could include a new device and/or dosage regimen, then they could make an appointment to see the practice nurse. Patients were also advised that they could direct any queries they had to their community pharmacist who would also be able to demonstrate the new device. The Panel queried whether the arrangements for patients in cohort 2 were acceptable given how important compliance and the correct use of devices was to the control of asthma.

The Panel noted Orion's campaign promoted a switch to Easyhaler devices on the basis of cost. In the Panel's view, the company must be especially vigilant to ensure that any therapeutic review offered in the same therapeutic field complied with Clause 18.4 and its supplementary information. There must be a clear, visible demarcation between any promotional activity and the offer and implementation of the therapeutic review. Were it otherwise, the review would be seen as a switching service contrary to Clause 18.4. The Panel noted its comments above about the representatives' briefing. In the Panel's view, some representatives would have been left with the unacceptable impression that the review was to be used as a vehicle to increase sales which was contrary to the Code. The Panel also noted the unacceptable impression given by the promotional leavepieces when left at a practice with the service leavepiece and the second patient cohort referred to in the protocol. In the Panel's view and on the balance of probabilities the combined effect of the above factors was that prescribers were more likely to switch patients to Easyhaler devices; the Panel ruled a breach of Clause 18.4 and thus of

Clause 18.1. The Panel considered that to provide representatives with materials which referred to switching and then ask them to leave material which introduced a therapy review programme meant that high standards had not be maintained. A breach of Clause 9.1 was ruled. The Panel noted that the complainant had made no specific allegation with regard to the conduct of any representative. In the Panel's view, by using the materials provided and introducing prescribers to the service, representatives had complied with their briefings and in that regard had not failed to maintain high standards. The Panel ruled no breach of Clause 15.2.

The Panel acknowledged the clinical value of a therapy review service for asthma patients and although it had particular concerns about cohort 2 (if the GP decided to include such a cohort in the review), it considered that on balance the respiratory review service had not been such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

During its consideration of this case the Panel had a number of concerns about the materials provided and the conduct of the respiratory review service. With regard to the materials, the Panel noted Orion's submission that the presentations at the May sales meeting and the respiratory review training presentation were not certified before use. Given that this matter was not the subject of the complaint, the Panel could not make any ruling upon it. The Panel also noted that the agreement between the service provider and Orion was a general service contract that the service provider used when it provided services to a range of commissioning organisations such as the NHS, research organisations and the pharmaceutical industry. Not all of the clauses within the contract were relevant to Orion. In the Panel's view this was unacceptable; if some of the clauses were not applicable they should at least have been scored out of the signed contract. It was impossible to know the exact details of what had been agreed between the parties.

The Panel was concerned that Orion appeared to take very little responsibility for the service provider pharmacists acting on its behalf. The Panel requested that Orion's attention be drawn to supplementary information in the Code which stated, *inter alia*, that service providers must operate to detailed written instructions provided by the company. Orion had stated that it did not provide any briefing documents to the service provider pharmacists. Although the company submitted that the pharmacists had an average of 7 years' post-graduate clinical experience, the Panel noted that in the briefing document given to them by the service provider it was stated 'Familiarise yourself with the dynamics of the BTS guidelines for asthma and NICE guidelines on COPD'. The same document provided a brief resumé of useful clinical information on various therapy options. In that regard the pharmacists did not appear to be respiratory specialists.

Complaint received **14 July 2014**

Case completed **27 October 2014**

CASE AUTH/2723/7/14

CLINICIAN v NAPP

Promotion of BuTrans

A consultant psychiatrist with an NHS trust, complained about a BuTrans (buprenorphine transdermal patch) advertisement and website created by Napp Pharmaceuticals which raised awareness of the difficulty of treating pain in patients with dementia. The complainant also provided a copy of a detail aid.

BuTrans was indicated for the treatment of non-malignant pain of moderate intensity when an opioid was necessary for obtaining adequate analgesia. BuTrans was not suitable for the treatment of acute pain.

The complainant submitted that agitation and aggression were particularly burdensome for carers. Agitation had multiple causes, one of which was pain. Better pain relief was likely to reduce agitation in dementia and a pain relieving patch made sense because compliance was easier.

The complainant quoted text from the www.butrans.co.uk website which he/she alleged implied that there was evidence to support the use of BuTrans in dementia which was misleading.

The complainant stated that the published evidence about the use of BuTrans in dementia derived from a single trial, various aspects of which had been published (Husebo *et al* 2011, Husebo *et al* 2014, and Sandvik *et al* 2014). In summary, patients were recruited on the basis that they were agitated, not because they had pain; only 57% were recorded as having clinically relevant pain. BuTrans was used as part of a stepped pain relief protocol in which patients first tried paracetamol, then opiate, then BuTrans, then pregabalin. The majority only took paracetamol. Of those allocated to the treatment arm (n=103), only 29 (28%) received a BuTrans patch. Some patients went straight onto the patch because of trouble swallowing but the three papers differed in their accounts of whether this applied to all of those who started the patch.

The complainant stated that mean scores for pain were not significantly different between control and BuTrans at week 2 or week 4 but were significantly different at 8 weeks with no correction for multiple comparisons. Nowhere was it stated how many of the 29 patients had pain and how many of those who did have pain responded to the patch and therefore the trial did not provide data that BuTrans had a beneficial effect on pain in patients with dementia. The fact that benefit only became apparent after 2 months, despite daily treatment, also raised questions as to the robustness of the findings.

As the presented data on the effect of the stepped protocol on agitation were not disaggregated by medicine it was impossible to know whether BuTrans had any effect on agitation. This was particularly the case for the 'aggressive behaviour' factor where significant levels were marginal. There was no evidence that BuTrans reduced the need for antipsychotics.

Given the low number of patients taking BuTrans in the study, it was hard to interpret the data on tolerability. However, 4 of the 29 patients dropped out because of side effects including femur fracture, drowsiness and nausea, local reaction to patch, appetite and eating disturbance. Other opiates such as tramadol also had adverse effects in dementia and worsened confusion. Confusion was listed as a common side effect in the BuTrans summary of product characteristics (SPC).

As a clinician who treated agitated patients with dementia, the complainant knew that Husebo *et al* suggested that analgesics might reduce agitation irrespective of whether patients had pain since inclusion criteria did not demand the presence of pain.

The complainant was concerned that the advertisement, in which the wording and the picture clearly indicated aggressive agitation, made a claim that BuTrans had an effect on agitation. Aggressive agitation of the type depicted was a relatively common problem for which doctors often felt compelled to prescribe. However, such patients would not be well served by a treatment which, if effective, took two months to work.

The wording of the promotional material was careful but in the complainant's view it was misleading as it elided the treatment of pain and agitation in a way which was beyond the evidence.

The detailed response from Napp is given below.

The Panel noted that it had been proposed that in some dementia patients the only way that they might be able to express pain was through agitation and aggression and that pain relief might in turn have a beneficial effect on such behaviour. The only clinical study used to support the use of BuTrans to treat pain in dementia patients was Husebo *et al* (2011) which set out to determine whether, over eight weeks, a systematic approach to the treatment of pain could reduce agitation in patients with moderate to severe dementia living in nursing homes. Although further details of the study were published in 2014 by Sandvik *et al* and Husebo *et al*, both postdated the material at issue; the website was approved in November 2013 and the advertisement and detail aid were approved in December 2013.

In Husebo *et al* (2011) nursing home residents were included in the study independent of painful diagnoses, presumed pain or ongoing pain treatment and assigned to a stepwise treatment group or to receive normal management. The ongoing pain treatment could include aspirin or anti-inflammatories provided that patients had been stable on these for four weeks before inclusion into the study. Use of analgesics as needed (other than paracetamol) was also permitted. Clinicians were advised to keep the prescription and dose of psychotropics unchanged where possible. Fifty nine percent of patients in the intervention group had a clinically relevant pain score of ≥3 on a pain scale. The stepwise treatment was step 1, paracetamol (maximum 3g/day), step 2, oral morphine (maximum 20mg/day), step 3, BuTrans (maximum 10µg/hour) and finally, oral pregabalin (maximum 300mg/day). Combination therapy was permitted if needed. The primary outcome measure was agitation as assessed by a nurses' rating questionnaire. Assessment of pain using the pain scale was a secondary outcome measure. Of the 175 patients assigned to the treatment group, 39 (22%) received BuTrans of whom 31 (18%) received the 5µg/hour patch and 8 (5%) received the 10µg/hour patch. The majority of patients (n=120, 69%) received paracetamol. The results showed that agitation was significantly reduced in the intervention group compared with the control group after eight weeks (p<0.001). The differences in pain scores between the control group and the intervention group were statistically significant at weeks 2, 4 and 8 in favour of intervention (p<0.001). The correlation between pain and aggression at week 8 was significant (p=0.01). Husebo *et al* (2011) did not examine between group differences in the intervention group but subsequent analysis by Sandvik *et al*, which was not available when the material at issue was approved, showed that treatment with BuTrans significantly decreased pain scores but not before week 8.

The Panel accepted that the treatment of pain in patients with dementia posed particular problems. The study used to support the use of BuTrans in the treatment of pain in dementia included patients who were presumed to be in pain given that they displayed behaviours such as agitation and aggression; 41% of patients in the intervention group did not have a clinically relevant pain score (≥3) at baseline. The primary outcome measure was not a reduction in pain but a reduction in agitation. Agitation was taken as a marker for pain but patients were not positively diagnosed as having pain. The Panel noted the licensed indication for BuTrans and in that regard it considered that there was no way of knowing if the 39 BuTrans patients included in Husebo *et al* had non-malignant pain of moderate intensity for which an opioid was necessary for obtaining adequate analgesia and that they did not have acute pain. The Panel considered that there was a difference between clinicians reporting clinical research or using a medicine in a particular patient group and a pharmaceutical company using such data to promote its medicine in that patient group. The Panel queried, irrespective of the results of Husebo *et al* (2011), whether the promotion of BuTrans in dementia patients without a positive diagnosis of non-malignant, moderate pain was in accordance with the particulars listed in the BuTrans SPC.

The Panel considered that there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia. The 39 BuTrans patients included in Husebo *et al* (2011) had not been positively diagnosed with non-malignant pain of moderate intensity such that they required an opioid nor was it clear that they did not have acute pain. Analysis of the study results published after the material at issue had been approved showed that the treatment effect of BuTrans was not apparent until week eight of the eight week study. The Panel thus considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine. A breach of the Code was ruled. The Panel considered that claims for the analgesic efficacy of BuTrans in such patients could not be substantiated. A breach of the Code was ruled. These rulings were upheld on appeal. The Appeal Board was particularly concerned about the safety of using BuTrans in this vulnerable patient group given that if they could not verbalise pain, they were unable to express and communicate side-effects. The Panel further considered that within the context of the BuTrans material at issue, the statement 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics' would be assumed to relate to BuTrans. There was no evidence that treatment with BuTrans limited the unnecessary use of antipsychotics. In that regard, the Panel considered that the statement was misleading by implication and could not be substantiated. Breaches of the Code were ruled. These rulings were upheld on appeal.

With regard to the advertisement, the Panel noted its general comments above about the material at issue. The Panel, however, did not consider that the advertisement promoted BuTrans for the treatment of agitation *per se*. On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients. In that regard the Panel did not consider that the advertisement was misleading. No breach of the Code was ruled. This ruling was upheld on appeal.

During its consideration of this case the Panel noted that all of the promotional material included the BuTrans product logo which consisted of the product name in logo type beneath which was stated, 'Buprenorphine Matrix Patch 5µg/h. 10µg/h, 20µg/h'. In that regard the Panel noted that the majority of the 39 BuTrans patients in Husebo *et al* (2011) had been treated with only the low dose patch; 8 patients had had the dose increased to the 10µg/h patch and no-one received the 20µg/h patch.

The Panel was extremely concerned about the material at issue which in its view did not promote the rational use of BuTrans and in that regard it particularly noted the claims in the detail aid and on the website that 'BuTrans makes sense in dementia' and that it was a 'sensible choice' in dementia.

The Panel queried how such a broad, unqualified claim could be made on the basis of treatment of 39 patients. In the Panel's view there was little evidence of the analgesic efficacy of BuTrans in patients with dementia and the Panel noted in particular comments by Husebo *et al* (2011) that it was possible that agitation (the primary outcome measure) declined as a result of patients being sedated following the use of opioid analgesics ie BuTrans or oral morphine (step 2 of the treatment protocol) and comments from Sandvik *et al* that the treatment effect of BuTrans was not apparent until week 8. The Panel also noted that side effects of BuTrans included confusion, agitation and anxiety. The Panel noted its comments above and considered that if its rulings of breaches of the Code were appealed, it would require, in accordance with Paragraph 7.1 of the Constitution and Procedure, the promotional campaign at issue to be suspended pending the final outcome of the case.

Overall, the Panel was concerned that the promotional material at issue was inappropriate. Promoting a medicine in a patient group in whom there was no robust evidence of efficacy was an extremely serious matter. The Panel decided to report Napp to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure for it to decide whether further sanctions were warranted.

The Appeal Board noted the Panel's concerns and rulings including that the Panel had required the material to be suspended pending the final outcome of the case. Given its rulings of breaches, the Appeal Board noted that the material at issue would now have to be withdrawn. The Appeal Board decided, in this instance, to take no further action in relation to the report from the Panel.

A consultant psychiatrist with an NHS Trust, complained about a BuTrans (buprenorphine transdermal patch) advertisement (ref UK/BUTR-13054b) and website (ref UK/BUTR-12036) created by Napp Pharmaceuticals Limited which referred to the difficulty of treating pain in patients with dementia. The complainant also provided a copy of a detail aid (ref UK/BUTR-13057).

BuTrans was indicated for the treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia. BuTrans was not suitable for the treatment of acute pain.

COMPLAINT

The complainant explained that patients with agitation in dementia were more vulnerable to overselling than any other group; fines of over $7 billion had been raised for the over promotion of antipsychotic and antiepileptic medicines by companies for that purpose.

The complainant noted that Napp had placed a full page advertisement for BuTrans in the BMJ which emphasised the medicine's role in dementia. The complainant submitted that Napp was engaged in a promotional campaign to raise awareness of the important and under-recognised problem of pain in dementia.

The complainant stated that agitation and aggression were particularly burdensome for carers. Agitation had multiple causes, one of which was pain. Better pain relief was likely to reduce agitation in dementia and a pain relieving patch made sense because compliance was easier.

The complainant quoted text from the www.butrans.co.uk website as follows along with the list of references:

> 'Pain in dementia is very real but remains significantly under-diagnosed and under-treated (Zwakhalen *et al* 2009, Closs *et al* 2004, Horgas and Tsai 1998 and Reynolds *et al* 2008). Behavioural changes, such as agitation and aggression, may be a patient's only way of showing they're in pain. But these same factors can make pain management even more challenging for family and carers (Cook *et al* 1999 and Sampson and Kitchen 2005).
>
> That's why the once-weekly ***BuTrans*** patch is a sensible choice in dementia.
>
> - It delivers convenient, well-tolerated and consistent relief for seven days, easing the daily pill burden on patients and their carers (BuTrans summary of product characteristics (SPC), Vadivelu and Hines 2008, Napp data on file and Plosker 2011)
> - It can improve treatment compliance compared with oral medication, offering effective long-term management of chronic pain (Plosker 2011 and Gallagher *et al* 2009)
> - As part of a step-wise approach to pain treatment, ***BuTrans*** was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care (Plosker 2011 and Husebo *et al* 2011)
> - Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics (Plosker 2011, Husebo *et al* 2011 and Banerjee 2009))
>
> Explore the website for more information on ***BuTrans***, or learn more about managing pain in dementia by using the external links below:
>
> - **Pain in dementia**
> - **BuTrans is a sensible choice in dementia**
> - **Pain assessment tool.'**

The complainant stated that the following sentences implied that there was evidence to support the use of BuTrans in dementia which was misleading:

> 'As part of a step-wise approach to pain treatment, BuTrans was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care (Plosker 2011 and Husebo *et al* 2011).

Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics.'

The complainant stated that the published evidence about the use of BuTrans in dementia derived from a single trial; various aspects of which had been published (Husebo *et al* 2011, Husebo *et al* 2014, and Sandvik *et al* 2014). In summary, patients were recruited into the trial on the basis that they were agitated, not because they had pain; only 57% were recorded as having clinically relevant pain. BuTrans was used as part of a stepped pain relief protocol in which patients first tried paracetamol, then opiate, then BuTrans, then pregabalin. The majority of patients only took paracetamol. The primary and secondary outcomes were based on reports from those involved in day-to-day care. Whilst attempts to blind the raters were made, no report was made of the success of this effort and carers would have clearly known if someone was treated with a patch or not. Of those allocated to the treatment arm (n=103), only 29 (28%) received a BuTrans patch. Some patients went straight onto the patch because of trouble swallowing but the three papers differed in their account of whether this applied to all of those who started the patch.

Mean scores for pain were not significantly different between control and BuTrans at week 2 or week 4 but were significantly different at 8 weeks with no correction for multiple comparisons. Nowhere in the publications was it stated how many of the 29 patients had pain and how many of those who did have pain responded to the patch and therefore the trial did not provide data that BuTrans had a beneficial effect on pain in patients with dementia. The fact that benefit only became apparent after 2 months, despite daily treatment, also raised questions as to the robustness of the findings.

As the presented data on the effect of the stepped protocol on agitation were not disaggregated by medicine it was impossible to know whether BuTrans had any effect on agitation. This was particularly the case for the 'aggressive behaviour' factor where significant levels were marginal. There was no evidence that BuTrans reduced the need for antipsychotics.

Given the low number of patients taking BuTrans in the study, it was hard to interpret the data on tolerability. However, 4 of the 29 patients dropped out because of side effects including femur fracture, drowsiness and nausea, local reaction to patch, appetite and eating disturbance. Other opiates such as tramadol also have adverse effects in dementia and worsen confusion. The complainant noted that confusion was listed as a common side effect in the BuTrans SPC.

As a clinician who treated agitated patients with dementia, the complainant knew that following wide publicity at the time, Husebo *et al* suggested that analgesics might reduce agitation irrespective of whether patients had pain since inclusion criteria did not demand the presence of pain.

The complainant stated that he/she had complained because his/her first impression of the advertisement, in which the wording and the picture clearly indicated aggressive agitation, was that it made a claim that BuTrans had an effect on agitation. Aggressive agitation of the type depicted was a relatively common problem for which doctors often felt compelled to prescribe. However, such patients would not be well served by a treatment which, if effective, took two months to work.

The wording of the promotional material was careful but in the complainant's view it was misleading as it elided the treatment of pain and agitation in a way which was beyond the evidence.

When writing to Napp, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Napp submitted that it took compliance very seriously and was naturally disappointed to learn that any of its materials should be the subject of a complaint from a health professional.

Napp submitted that it had taken into consideration the complainant's comments, although it was difficult to identify the precise focus of the complaint; with respect to the Code Napp considered that there were two promotional items at issue. The first was the BuTrans advertisement in the BMJ and the second was the BuTrans pain in dementia webpage.

Napp submitted that it was established that pain in patients who suffered from dementia was an under recognised and undertreated condition:

- People with dementia were as likely to feel pain to the same extent as individuals without dementia, but might have lost the verbal skills necessary to express and communicate their pain (Herr 2006). As a result it could be difficult for carers to identify whether patients were in pain. Indeed people with dementia took fewer analgesics and reported less pain compared with their non-cognitively impaired peers (Reynolds *et al* 2008, Achterberg *et al* 2013 and Pieper *et al* 2013).
- A 2009 report, commissioned by the Department of Health (DoH), highlighted the overuse of antipsychotics to treat behavioural and psychological disturbances (such as agitation and aggression) in dementia. The report gave recommendations to reduce their use given that it was estimated that annually they caused more than 1,620 cerebrovascular adverse events and 1,800 deaths (Banerjee 2009).
- The assessment of pain in dementia patients was particularly challenging and behavioural pain scales had been specifically developed to assess pain in dementia patients. Three behaviours, 'pain noises', 'facial expression' and 'defence' behaviours, were specifically examined in the MOBID-2 pain scale (Husebo *et al* 2011, Husebo *et al* 2014 and Sandvik *et al* 2014). Facial expression was used to denote movement caused by pain,

expressed by the words: grimacing, frowning, tightening mouth and closing eyes.

- The National Institute for Health and Care Excellence (NICE) Dementia Guidelines, the 2009 DoH report on the use of antipsychotics in dementia and current guidelines from the Alzheimer's Society recommended that the first line management of behavioural and psychological disturbances in dementia should be a detailed assessment to identify any treatable causes such as pain. Indicators for pain in a person with dementia included either withdrawn or disturbed behaviour, which could include agitation and aggression.

Napp submitted that the treatment of pain in dementia had been subject to several reviews which concluded that the 'available evidence suggests that (pain) interventions targeting behaviour, and (behavioural) interventions targeting pain are effective in reducing pain and behavioural symptoms in dementia' (Achterberg *et al* 2013 and Pieper *et al* 2013). This included a study (discussed by the complainant) that demonstrated the treatment of pain in dementia could reduce behavioural symptoms including agitation and aggression (Husebo *et al* 2011).

Husebo *et al* (2011) was published in the BMJ and further data analyses from this study was published in 2014 (Husebo *et al* and Sandvik *et al*).

- The study was a cluster randomised controlled trial published in a recognised peer-reviewed journal and used a well validated tool (Cohen-Mansfield Agitation Inventory) to evaluate agitation in dementia patients.
- The objective of this study was to determine whether a systematic approach to the individualised treatment of pain could reduce agitation in people with moderate to severe dementia living in nursing homes.
- There were four steps in the pain management protocol: 1, paracetamol (maximum 3g/day), 2, morphine (maximum 20 mg/day), 3, BuTrans (maximum 10 micrograms/hour) and 4, pregabalin (maximum 300 mg/day).
- The study demonstrated that a step-wise approach to pain management in dementia patients significantly improved their pain and behavioural disturbances, including agitation and aggression.

Napp submitted that BuTrans was a long-lasting analgesic in the form of a transdermal patch containing the opioid buprenorphine, available in three strengths (5, 10 & 20 micrograms/hour) and provided pain relief for up to seven days. BuTrans was licensed for the treatment of non-malignant pain of moderate intensity when an opioid was necessary for obtaining adequate analgesia and its use was well established in the UK since launch in 2005.

Dementia patients were often elderly and suffered from a number of chronic painful co-morbidities (e.g. musculoskeletal pain, old fractures and arthritis). BuTrans was therefore an appropriate option for treating pain in this patient group because:

- The prolonged release formulation provided consistent analgesia for up to seven days
- BuTrans did not require dose adjustment in the elderly nor in patients with severe renal impairment.
- A patch formulation could reduce the pill burden on patients and was a convenient alternative for those who had difficulty swallowing (Plosker 2011).

In light of the background provided above, the focus of the materials at issue was to:

- highlight the difficulty in assessing pain in patients with dementia
- raise awareness of the common signs that could indicate pain (e.g. agitation and aggression).
- demonstrate BuTrans was an appropriate option to treat chronic pain in such patients.

Having considered the complaint about the BMJ advertisement in terms of Clauses 7.2 and 7.4, Napp disagreed with the allegation that it was misleading and submitted that the claims could be substantiated.

Napp submitted that the advertisement did not state that BuTrans had an effect on agitation. The imagery and accompanying text combined, placed a clear and explicit emphasis on pain management in dementia and in this respect BuTrans was a well-established analgesic, licensed for the treatment of moderate pain.

The supporting rationale for Napp's position was:

- The complainant had recognised in his/her opening paragraphs that pain in dementia was an 'important and under-recognised problem'. As acknowledged in the NICE guidelines on dementia (NICE CG42), the DoH report (Bannerjee 2009) and the Alzheimer's Society Report (Alzheimer's Society 2011) there was an established link between pain and behavioural disturbances in dementia, because these patients often found it hard to express themselves verbally. This could manifest itself in a number of ways including facial expressions denoting agitated, aggressive or challenging behaviour.
- The focus of the advertisement was on the management of pain in line with Napp's licensed indication, which stated that BuTrans was indicated for the treatment of moderate pain.
- The advertisement was intended to portray the facial expression of a patient in pain who, because of his dementia, was only able to express this through agitation and verbal aggression. Feedback from health professionals, including GPs, geriatricians and nurses during the development of this material was that the imagery was memorable, evocative and led to immediate patient identification for many.
- The advertisement text made no claim for BuTrans in the treatment of agitation in dementia patients. The emphasis of the text was on pain management; 'Agitation and aggression' was used only once at the start but specifically in the context of describing how patients with dementia could struggle to express that they were in pain.

In contrast 'pain' or 'analgesia' were used five times to emphasise that the advertisement was about pain management.
- The prominent strap line 'Dementia hurts enough without pain' underneath the image further stated the advertisement's focus was on pain management and not on agitation.
- The advertisement had comprehensive information for prescribers to be well informed about the use of BuTrans in the treatment of pain as clearly stated in the prescribing information.

The text and image taken as a whole clearly focussed on the use of BuTrans for pain management and not for agitation. The use and efficacy of BuTrans for the treatment of pain was well established and capable of substantiation. Therefore, Napp disagreed that there had been a breach of Clause 7.2 or 7.4.

With regard to the complaint about the BuTrans pain in dementia webpage in terms of Clauses 7.2 and 7.4, Napp disagreed with the allegation that the sentence referred to by the complainant, 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics' was misleading and submitted that the claims were capable of substantiation.

Napp submitted that it had not stated that BuTrans had supporting evidence for treating agitation and aggression in dementia.

The supporting rationale for Napp's position was:

- That it clearly stated that a step-wise approach to pain management was carried out (using various analgesics) and that BuTrans, which was licensed for moderate pain, was a part of that approach. Napp submitted that it did not claim that BuTrans directly improved agitation and aggression in dementia, nor did it claim that BuTrans alone was responsible for the observed finding.
- Therefore, as suggested by the complainant, the wording was indeed carefully chosen to reflect in the first instance that a step-wise approach to pain management was used, whilst secondly reflecting that BuTrans was part of (i.e. 'was associated with') the step-wise approach to the management of pain.
- Furthermore, the context of the webpage as a whole was clearly about the challenge of identifying and treating pain in patients with dementia, and that BuTrans was an appropriate choice for treating that pain.

Based on the above Napp disagreed that it had been misleading about the use of BuTrans in the treatment of agitation and aggression in dementia.

- Napp noted that the complainant highlighted Husebo *et al* (2011) as a key piece of evidence, from which he/she alleged that Napp had made misleading claims for BuTrans with respect to agitation and aggression. As discussed above, this study was well designed and published in a peer reviewed journal (BMJ).
- The study demonstrated that following a step-wise approach to pain management in dementia patients could significantly improve pain and behavioural disturbances, including agitation and aggression. BuTrans, which was licensed in the treatment of moderate pain was used at step three.
- The complainant stated that 28 patients received BuTrans, however 37 patients were treated with BuTrans (Husebo *et al* 2011).

Napp submitted that it had not stated that BuTrans had supporting evidence for treating agitation and aggression in dementia. Napp clearly stated that a step-wise approach to pain management was carried out, that BuTrans (which was licensed for moderate pain) was a part of this approach, and that such an approach reduced agitation and aggression, all of which could be substantiated.

Napp therefore denied a breach of Clause 7.2 or 7.4.

Having considered the complaint about the BuTrans dementia webpage in terms of Clause 7.2 and 7.4, Napp disagreed with the allegation that the sentence on the webpage, 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics' was misleading and believed that the claims made could be substantiated.

The supporting rationale for Napp's position was as follows:

- Napp submitted that it had not stated that BuTrans was associated with reduced antipsychotic usage. BuTrans was not mentioned in the sentence. Therefore, it denied that it had claimed that use of BuTrans to treat pain in dementia could limit unnecessary antipsychotic usage.
- In the wider context of the webpage text, it was clear that Napp had focussed on the appropriate management of pain in patients with dementia. Therefore, Napp submitted that it had not misled about the effect of BuTrans on antipsychotics.
- Napp submitted that as stated above, it was an established problem that antipsychotics were overused to treat behavioural and psychological disturbances, including agitation and aggression, in dementia (Bannerjee 2009). This overuse of antipsychotics was estimated to cause more than 1,620 cerebrovascular adverse events and 1,800 deaths per year (Bannerjee 2009).
- It was therefore recommended that the first line management of behavioural and psychological disturbance should be a detailed assessment to identify any treatable causes, which included pain, before the use of antipsychotics was considered (Bannerjee 2009, NICE CG42, Alzheimer's Society 2011).
- It was clear from the clinical guidelines that if improved treatment approaches to pain could reduce pain-related behavioural disturbances (Husebo *et al* 2011), then this could reduce the need for unnecessary antipsychotics.

Napp submitted that in light of the above clinical guidelines, the sentence 'Effectively managing pain in dementia can help reduce pain-related

behavioural disturbances, limiting unnecessary use of antipsychotics' could be substantiated. Therefore, based on the above, Napp denied a breach of Clause 7.2 or 7.4.

Finally, Napp noted that the complainant stated in his/her introductory paragraphs that Napp 'was engaged on a promotional campaign to raise awareness of the important and under-recognised problem of pain in dementia' and that 'agitation and aggression were particularly burdensome for carers. Agitation had multiple causes, one of which was pain. Better pain relief was likely to reduce agitation in dementia and a pain relieving patch made sense because compliance was easier'. In this respect the complainant had provided an accurate description of the intent and purpose of the content of the advertisement and web page in question.

PANEL RULING

The Panel noted that BuTrans was indicated for the treatment of non-malignant pain of moderate intensity when an opioid was necessary for obtaining adequate analgesia. BuTrans was not suitable for the treatment of acute pain.

The Panel noted that Napp had confined the comments in its response to the advertisement and the web page. The complainant, however, had provided a copy of the detail aid which in turn had been provided to Napp. In the Panel's view the detail aid was within the scope of the complaint.

The Panel noted that it had been proposed that in some dementia patients with impaired language and abstract thinking, the only way that they might be able to express pain was through agitation and aggression and that pain relief might in turn have a beneficial effect on such behaviour. The only clinical study used to support the use of BuTrans to treat pain in dementia patients was Husebo *et al* (2011) which set out to determine whether, over eight weeks, a systematic approach to the treatment of pain could reduce agitation in patients with moderate to severe dementia living in nursing homes. Although further details of the study were published in 2014 by Sandvik *et al* and Husebo *et al*, both postdated the material at issue; the website was approved in November 2013 and the advertisement and detail aid were approved in December 2013.

In Husebo *et al* (2011) nursing home residents were included in the study independent of painful diagnoses, presumed pain or ongoing pain treatment and assigned to a stepwise treatment group or to receive normal management. The ongoing pain treatment could include aspirin or anti-inflammatories provided that patients had been stable on these for four weeks before inclusion into the study. Use of analgesics as needed (other than paracetamol) was also permitted. Clinicians were advised to keep the prescription and dose of psychotropics unchanged where possible. Fifty nine percent of patients in the intervention group had a clinically relevant pain score of ≥3 on the mobilization-observation-behaviour-intensity-dementia-2 (MOBID-2) pain scale at baseline. MOBID-2 was an observational pain scale which assessed pain intensity based upon a patient's immediate pain behaviour such as vocalisation, facial expression and use of defensive body positions. The stepwise treatment was step 1, paracetamol (maximum 3g/day), step 2, oral morphine (maximum 20mg/day), step 3, BuTrans (maximum 10µg/hour) and finally, oral pregabalin (maximum 300mg/day). Combination therapy was permitted if needed. The primary outcome measure was agitation as assessed by a nurses' rating questionnaire. Assessment of pain using the MOBID-2 pain scale was a secondary outcome measure. Of the 175 patients assigned to the treatment group, 39 (22%) received BuTrans of whom 31 (18%) received the 5µg/hour patch and 8 (5%) received the 10µg/hour patch. The majority of patients (n=120, 69%) received paracetamol. The results showed that agitation was significantly reduced in the intervention group compared with the control group after eight weeks ($p<0.001$). The differences in MOBID-2 scores between the control group and the intervention group were statistically significant at weeks 2, 4 and 8 in favour of intervention ($p<0.001$). The correlation between pain and aggression at week 8 was significant ($p=0.01$). Husebo *et al* (2011) did not examine between group differences in the intervention group but subsequent analysis by Sandvik *et al*, which was not available when the material at issue was approved, showed that treatment with BuTrans significantly decreased MOBID-2 pain scores but not before week 8.

The Panel accepted that the treatment of pain in patients with dementia posed particular problems both for the patient and the care givers. The study used to support the use of BuTrans in the treatment of pain in dementia included patients who were presumed to be in pain given that they displayed behaviours such as agitation and aggression; 41% of patients in the intervention group did not have a clinically relevant score (≥3) on the MOBID-2 pain scale at baseline. The primary outcome measure was not a reduction in pain but a reduction in agitation. Agitation was taken as a marker for pain but patients were not positively diagnosed as having pain. The Panel noted the licensed indication for BuTrans and in that regard it considered that there was no way of knowing if the 39 BuTrans patients included in Husebo *et al* had non-malignant pain of moderate intensity for which an opioid was necessary for obtaining adequate analgesia and that they did not have acute pain. The Panel considered that there was a difference between clinicians reporting clinical research or using a medicine in a particular patient group and a pharmaceutical company using such data to promote its medicine in that patient group. The Panel queried, irrespective of the results of Husebo *et al* (2011), whether the promotion of BuTrans in dementia patients without a positive diagnosis of non-malignant, moderate pain was in accordance with the particulars listed in the BuTrans SPC.

The Panel noted that the complainant had stated that the following sentences on the BuTrans website implied that there was evidence to support the use of BuTrans in dementia which was misleading:

> 'As part of a step-wise approach to pain treatment, BuTrans was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care (Plosker 2011 and Husebo *et al* 2011)
>
> Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics.'

The Panel considered that there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia. The 39 BuTrans patients included in Husebo *et al* (2011) had not been positively diagnosed with non-malignant pain of moderate intensity such that they required an opioid nor was it clear that they did not have acute pain. Analysis of the study results published after the material at issue had been approved showed that the treatment effect of BuTrans was not apparent until week eight of the eight week study. The Panel thus considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine. A breach of Clause 7.2 was ruled. The Panel considered that claims for the analgesic efficacy of BuTrans in such patients could not be substantiated. A breach of Clause 7.4 was ruled. These rulings were appealed. The Panel further considered that within the context of the BuTrans material at issue, the statement 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics' would be assumed to relate to BuTrans. There was no evidence that treatment with BuTrans limited the unnecessary use of antipsychotics. In that regard, the Panel considered that the statement was misleading by implication and could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. These rulings were appealed.

With regard to the advertisement, the Panel noted its general comments above about the material at issue. The Panel, however, did not consider that the advertisement promoted BuTrans for the treatment of agitation *per se*. On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients. In that regard the Panel did not consider that the advertisement was misleading. No breach of Clause 7.2 was ruled. This ruling was appealed.

During its consideration of this case the Panel noted that all of the promotional material included the BuTrans product logo which consisted of the product name in logo type beneath which was stated, 'Buprenorphine Matrix Patch 5µg/h. 10µg/h, 20µg/h'. In that regard the Panel noted that the majority of the 39 BuTrans patients in Husebo *et al* (2011) had been treated with only the low dose patch; 8 patients had had the dose increased to the 10µg/h patch and no-one received the 20µg/h patch.

The Panel was extremely concerned about the material at issue which in its view did not promote the rational use of BuTrans and in that regard it particularly noted the claims in the detail aid and on the website that 'BuTrans makes sense in dementia' and that it was a 'sensible choice' in dementia. The Panel queried how such a broad, unqualified claim could be made on the basis of treatment of 39 patients. In the Panel's view there was little evidence of the analgesic efficacy of BuTrans in patients with dementia and the Panel noted in particular comments by Husebo *et al* (2011) that it was possible that agitation (the primary outcome measure) declined as a result of patients being sedated following the use of opioid analgesics ie BuTrans or oral morphine (step 2 of the treatment protocol). However the authors noted that only 25.6% of patients were treated with a sedative agent and that only 3 were excluded because of drowsiness or nausea. Sandvik *et al* reported that the treatment effect of BuTrans was not apparent until week 8 and also noted that due to the metabolic pathway of buprenorphine, careful monitoring was required in patients with hepatic impairment, and this was an important consideration when prescribing to patients with dementia. The Panel noted that a common (≥1/100, <1/10) side effect listed in the BuTrans SPC was confusion, uncommon (≥1/1000, <1/100) side effects included agitation and anxiety and rarely (≥1/10,000, <1/1000) the medicine could cause psychotic disorders. The Panel noted its comments above and considered that if its rulings of breaches of the Code were appealed, it would require, in accordance with Paragraph 7.1 of the Constitution and Procedure, the promotional campaign at issue to be suspended pending the final outcome of the case.

Overall, the Panel was concerned that the promotional material at issue was inappropriate as discussed above. Promoting a medicine in a patient group in whom there was no robust evidence of efficacy was an extremely serious matter. The Panel decided to report Napp to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure for it to decide whether further sanctions were warranted.

APPEAL FROM THE COMPLAINANT

The complainant appealed the Panel's ruling of no breach of Clause 7.2 concerning the advertisement and noted that the Panel's comments also suggested that there might have been a breach of Clause 3.2.

The complainant noted that Clause 7.2 stated:

> 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis.
>
> Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.'

The complainant gave the following as his grounds for appeal:

1 The complainant disagreed with Napp's submission that '... the advertisement did not state that BuTrans had an effect on agitation. The imagery and accompanying text combined placed a clear and explicit emphasis on pain management in dementia ...'. The Panel ruled that it 'did not consider that the advertisement promoted BuTrans for the treatment of agitation *per se*'. However, the devil here was in the '*per se*'. The complainant alleged that the words and the image conflicted; the words talked about pain but the image depicted aggression, not pain.

a) Indeed, Napp clearly stated that the image depicted agitation and aggression: 'The advertisement was intended to portray ... agitation and verbal aggression'. (The omitted words here were 'the facial expression of a patient in pain who because of his dementia, was only able to express this through'). Napp also submitted that feedback from professionals was that the '... imagery was memorable, evocative and led to immediate patient identification for many'. The complainant agreed with this and alleged that this was exactly the problem. Most agitation and aggression was nothing to do with pain (as evidenced by the fact that only 41% of those in the study had significant clinical pain). A less misleading image would make clear the primary role of pain rather than just depicting agitation/aggression.

b) The complainant alleged that it might sometimes be reasonable for images to depict downstream symptomatic benefits of a primary proven effect. However, there were two problems with this. Firstly, this was different from depicting an indication which was not part of the licence. This was the fundamental error that led Pfizer and others to incur such huge fines when they promoted their medicines for agitation and psychosis in dementia. (Incidentally, the quality of the evidence for a benefit of antipsychotics on agitation in dementia was higher than that for BuTrans). Secondly, the primary effect was not proven: as the Panel stated, '... there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia'.

2 The complainant alleged that there was internal inconsistency in the ruling because 'The Panel ruled the website in breach because it considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine'. However, exactly the same materials pertained to the BMJ advertisement. Similar wording, which was criticised by the Panel in respect of the website, was used in the advertisement; including the notion that it 'makes sense' ('That's why BuTrans transdermal patches make sense').

3 The complainant noted the Panel's statement that 'On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'. However, the Panel also 'considered that there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia'. It also 'considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine'. This might, therefore, amount to a breach of Clause 3.2 ('The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics') as well as Clause 7.4. This possibility did not appear to have been considered.

4 The complainant alleged that the number of patients treated with BuTrans in the study was difficult to ascertain. Napp referred to 37. Sandvik *et al* stated: 'Step 3, the buprenorphine transdermal patch, was administered to 29 patients (17.7%), and the buprenorphine dosage was increased in an additional eight participants. In total, 37 participants were treated with buprenorphine transdermal patch, of whom 9 received the patch alone, with no other medication, due to swallowing issues'. Husebo *et al* stated: 'Thirty one participants (18%) received step 3 (buprenorphine transdermal patch), and in addition eight participants (5%) the dosage was increased'. This suggested that 8 patients in the intervention arm (ie 22%) were already taking buprenorphine before the study started. It was not known how many patients in the control arm were already taking buprenorphine.

5 The complainant alleged that whilst the intent and purpose of the advertisement was understandable, the claims went beyond the evidence and were misleading.

COMMENTS FROM NAPP

Napp submitted that the specific grounds stated by the complainant for the appeal had been addressed in its previous submissions hence it referred to its previous submissions.

Napp's responded to the complainant's appeal using the same numbering as above.

1/1a Napp noted the allegation that the words and image conflicted. The words talked about pain but the image was not one of pain. It depicted aggression, not pain. Napp referred to its response to the complainant and its appeal on this point.

Napp submitted that the link between pain and aggression was very clear from the available literature (ie not just Husebo *et al*) but for the avoidance of any doubt, it had never claimed that aggression in patients with dementia was caused exclusively by pain. The advertisement was intended to bring to the attention of clinicians the need to consider pain in patients with dementia who became agitated. Pain

scales developed for the assessment of pain in dementia patients with severe cognitive impairment (who were unable to adequately verbalise their pain) included behavioural assessments. This again highlighted that a behavioural change might be due to pain as part of a differential diagnosis.

Napp noted that a complainant had the burden of proving his/her complaint on the balance of probabilities, as stated in the introduction of the Constitution and Procedure. The Panel ruled '... On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'. In that regard, the Panel did not consider the advertisement was misleading. Napp firmly maintained that the combination of text and imagery in the advertisement was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine, as required under Clause 7.2.

1b Napp submitted that the complainant's comment about imagery had been dealt with in its response in the above.

With respect to the complainant's comments about the therapeutic indication of BuTrans, Napp referred to its appeal.

2 Napp agreed that there was a potential inconsistency in the Panel's rulings. However, Napp now understood that the Panel ruled the advertisement not to be in breach of Clause 7.2 on the specific point about being misleading as to the promotion of BuTrans in agitation, but its general comments about the evidence base in pain made in the context of the webpage applied equally to the advertisement. Napp had addressed this in its appeal and in the above.

3 Napp referred to its response to point 1a above. Napp had been asked by the PMCPA not to respond to a complaint under Clause 3.2 as it was not within the scope of the complaint.

4 Whilst Napp agreed that the number of dementia patients treated with BuTrans was difficult to ascertain depending on which paper was considered, this was 39 patients in Husebo *et al* (2011) which was cited in the advertisement: 'Thirty one participants (18%) received step 3 (buprenorphine transdermal patch), and in addition eight participants (5%) the dosage was increased'. However, Napp was unclear as to the specific relevance of this to the complainant's appeal.

Napp noted that five references were cited in the BMJ advertisement and not solely the Husebo *et al* (reference 4). These references taken together when considering the advertisement supported the claims:

- Reference 1 (Cook *et al* 1999) 'Pain among people with cognitive impairment can also lead to increased care demand, as cognitive impairment is associated with the presence of depression and challenging behaviours, including aggression and '"disruptive" vocalizations'
- Reference 2 the BuTrans SPC, with licence information for clinicians
- Reference 3 (Plosker 2011) a review article of BuTrans for treatment of pain: 'As noted in section 3.3 [of this review article], the pharmacokinetic profile of buprenorphine is not significantly altered by renal impairment or advanced age, and dosage adjustments of transdermal buprenorphine are not required in these patient populations (section 6 [of this review article]). On the basis of these properties, a recent European consensus statement recommended transdermal buprenorphine as a first-line opioid for chronic pain in elderly patients'
- Reference 5 (Vadivelu *et al* 2008) a review article of the management of chronic pain in the elderly using transdermal buprenorphine including BuTrans: described the advantages and disadvantages of transdermal buprenorphine, including patients with dementia.

5 Napp submitted that it was rational and clinically appropriate to promote BuTrans for the treatment of moderate, chronic pain in dementia patients. Napp noted that the complainant believed that the intent and purpose of the advertisement was understandable. This intent was clearly conveyed in the advertisement, since the text and image taken as a whole clearly focussed on the use of BuTrans for pain management and not for agitation. Napp disagreed with the complainant's assertion that the claims went beyond the evidence and that they were misleading.

To conclude, Napp took compliance very seriously and felt strongly that the BuTrans advertisement was appropriate given its response.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant noted Napp's submission that the reasonable impression to be obtained from the materials was that the advertisement made claims for the use of BuTrans in the treatment of pain (and not for the direct treatment of agitation or aggression). The Panel had noted that 'On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'.

The complainant stated that his appeal against this ruling was on two grounds: firstly, if one accepted that this was a promotion for pain in dementia, this claim was not substantiated at the time, and had not been subsequently substantiated and secondly, clinicians who dealt with aggressive patients would strongly recognise the image and would think that it was promoting for aggression.

1 Promotion of BuTrans for pain

The complainant noted that Napp had argued that it was not necessary to provide evidence of benefit in the specific instance of pain being discussed (ie in dementia) on the grounds that it fell within its current authorization. 'Pain in patients who suffer from dementia represents a population with chronic pain and was therefore within our licensed indication. Dementia is a co-morbidity to chronic pain rather than dementia being a specific pain syndrome'.

However, the complainant alleged that there was a clear difference between the marketing authorization and whether an advertisement was misleading. If there was an overwhelming volume of high quality evidence that, in a particular population with pain, BuTrans had no beneficial effect, then promotion of BuTrans for use specifically in that population would be misleading. There must be a point at which the promotion was misleading if it was not supported by the evidence – that was, if it could not be substantiated.

The complainant alleged that a clinician reading the advertisement would reasonably assume that given the focus on dementia, there was relevant evidence for benefit on pain in patients with dementia; and that the studies of dementia patients which were cited supported that contention.

The complainant agreed with Napp that the different rulings on the advertisement and on the other material resulted in a degree of internal inconsistency. In particular, the issue of whether the material could be substantiated was broadly similar in the advertisement/website since it was based on the same evidence.

The complainant shared the Panel's view that '… there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia.' and that '… the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine'.

The complainant alleged that when the advertisement was approved, the published evidence was such that even a diligent clinician could not access any evidence relating to the benefit of BuTrans on pain in dementia. The only study with any data on BuTrans for patients with dementia was Husebo *et al* (2011). The inclusion criteria were related to agitation and not to pain. Many patients did not have significant pain on the MOBID-2 pain scale (which assessed pain which was not verbally expressed). There was no separation of the data on pain into those with or without clinically significant pain. Nor was data about paracetamol disaggregated from that for BuTrans.

The complainant noted that following the publication of further data in Husebo *et al* (2014) and Sandvik *et al* (2014), it was now known that BuTrans had no benefit on pain before 8 weeks, despite the fact that buprenorphine levels reached a steady state within a few days. This, coupled with the absence of pain data on patients who had not already been receiving BuTrans, the small sample size of 29 who were not taking BuTrans before the trial started, and the lack of control for multiple comparisons, meant that the assertion in Sandvik *et al* (2014) of a demonstration of efficacy on pain at 8 weeks did not, even now, have a 'sound statistical basis' (Figure 5 from Sandvik *et al* 2014). Even if the effect at week 8 was real, it was hard to see how the effect of a patch, which resulted in plateau levels within a few days, was delayed for nearly 2 months.

The complainant stated that the references cited in support of a promotion must support the point being made in the promotion if the advertisement was not to be 'misleading by implication'. Husebo *et al* (2011) was cited throughout the promotional campaign including the advertisement (as reference 4).

The complainant alleged that if the campaign was intended to increase awareness of the possibility that treating pain might reduce agitation, then the above graph implied that paracetamol, not BuTrans, should have been the suggested treatment option (notwithstanding Buffum *et al* 2004 – see below). The American Geriatric Society recommended paracetamol as first line treatment for pain in dementia.

2 Promotion of BuTrans for agitation

The complainant alleged that Napp had denied that the advertisement promoted BuTrans for agitation. However, Napp explicitly stated that the image was intended to convey aggressive agitation: 'The advertisement was intended to portray ... agitation and verbal aggression'. (The omitted words were 'the facial expression of a patient in pain who because of his dementia, was only able to express this through').

The complainant stated that the key point was that, for practising clinicians leafing through the BMJ, the impact of the striking image and the aggression conveyed by the strapline 'You can stick your tablets' overwhelmed the pain message. Clinicians would assume that the image depicted the sort of patient for whom the medicine was being promoted. It was difficult to avoid the implication that aggression was the target of the treatment, especially on a cursory reading. This impression was particularly heightened by the phrase '… easing the burden on patients **and their carer too**' (emphasis added). The effect of agitated behaviour, and aggression in particular, on carer burden was a major concern for prescribers. The impression that the target was agitation was reinforced by reference in the sales aid and website to the potential for reducing antipsychotic use.

The complainant alleged that there was no evidence from Husebo *et al* (2011), Husebo *et al* (2014), Sandvik *et al* or indeed any other trial, to show that opiates had a benefit on agitation in dementia. Whilst Husebo *et al* (2011) showed that

stepped analgesia might be of benefit, no data was presented to show that the introduction or increase of BuTrans reduced agitation any more than paracetamol. Therefore, if the image and words together were considered to promote BuTrans for agitation, they did not clearly reflect the evidence, misled by implication and were not substantiable. If the promotion was merely about compliance in dementia, or compliance in pain in dementia, it did not need to include such a striking image of aggression.

Thus, the complainant alleged that even if the image and words together were not considered to promote BuTrans for agitation, the image and words represented an undue emphasis on agitation. They also made the advertisement ambiguous as to the indication for which BuTrans was promoted.

APPEAL FROM NAPP

Napp confirmed that it had suspended the campaign materials pending the outcome of the appeal.

Napp submitted that was proud to be a leader in pain management and took the responsibility of promoting its analgesics very seriously to ensure clinicians were best informed to prescribe them appropriately. During the development of the campaign Napp was advised by a panel of health experts in both pain management and dementia. Napp refuted the Panel's rulings and firmly believed that it was appropriate to promote BuTrans for the treatment of pain in dementia.

Napp reiterated that it understood that the complaint was focussed on two materials – specifically the BMJ advertisement and the pain in dementia webpage – and Napp was asked to consider the complaint in terms of Clauses 7.2 and 7.4.

Napp interpreted the complaint as follows:

The BMJ advertisement was misleading because it claimed that BuTrans had a direct effect on agitation, and this was not capable of substantiation.

The pain in dementia webpage was misleading because, again, it claimed that BuTrans had a direct effect on agitation and aggression and that its use could lead to reduced use of antipsychotics, and neither of these were capable of substantiation. The complaint referred to the following two statements on the webpage:

> 'As part of a step-wise approach to pain treatment, BuTrans was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care (Husebo *et al* 2011).'
>
> 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics.'

Napp denied that it was misleading in the manner described above. As previously explained the intent behind, and the reasonable impression to be obtained from the materials was that:

- The advertisement made claims for the use of BuTrans in the treatment of pain (and not for the direct treatment of agitation or aggression)
- The webpage statement which referenced Husebo *et al* (2011) was a general statement focused on the step-wise management of pain (for which BuTrans was an appropriate option)
- The webpage statement about antipsychotic use was again a general statement focussed on the potential reduction in the amount of antipsychotic prescriptions if pain was properly managed and BuTrans itself was not claimed to cause a reduction in antipsychotic use. Furthermore, Napp submitted that the claims could be substantiated. Napp thus denied breaches of Clauses 7.2 and 7.4.

1 BMJ advertisement

Napp noted that no breach of Clause 7.2 was ruled. The Panel '…did not consider that the advertisement promoted BuTrans for the treatment of agitation *per se*. On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'. The Panel did not comment in relation to Clause 7.4 but Napp noted the broader comments made about the promotion of BuTrans in the treatment of pain in patients with dementia in point 3 below.

2 Pain in dementia webpage

a) 'As part of a step-wise approach to pain treatment, BuTrans was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care'.

Napp noted that the Panel ruled a breach of Clauses 7.2 and 7.4. However, the Panel´s ruling of misleading was not on the basis that Napp had claimed that BuTrans had a direct effect on agitation and aggression, as Napp had interpreted the complaint. Rather, the Panel stated that 'use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine' and 'the analgesic efficacy of BuTrans in such patients could not be substantiated'.

b) 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics'.

Napp noted that the Panel ruled breaches of Clauses 7.2 and 7.4. The Panel considered that '… within the context of the BuTrans material at issue [the statement above] would be assumed to relate to BuTrans', 'there was no evidence that treatment with BuTrans limited the unnecessary use of antipsychotics' and 'the statement was misleading by implication and could not be substantiated'.

3 Report to the Appeal Board

Napp noted that the Panel had made a number of general comments about the materials used in the campaign. The Panel considered that the BuTrans sales aid was part of the original complaint. This material was duly considered in this response in light of the general comments made by the Panel below. However, Napp submitted that there was no specific discussion or complaint about the sales aid in the complaint.

Napp noted that the Panel: stated in its ruling that the materials at issue 'did not promote the rational use of BuTrans'; queried how the broad, unqualified claims 'BuTrans makes sense in dementia' and BuTrans was a 'sensible choice' in dementia could be made on the basis of treatment of 39 patients and was concerned that the promotional material at issue was 'inappropriate' and that 'promoting a medicine in a patient group in whom there was no robust evidence of efficacy was an extremely serious matter'.

Napp submitted that as it had been reported to the Appeal Board and given the seriousness of the allegations made in relation to the 'pain in dementia' campaign as a whole, its response was in two parts. Part 1 dealt with Panel ruling 1 and the reasons for the report to the Appeal Board whilst Part 2 dealt with Panel ruling 2a) and ruling 2b) (defined above).

Background to BuTrans

Napp submitted that BuTrans was a prescription only analgesic which contained the active medicine buprenorphine within a transdermal patch. When attached to the upper body, the medicine slowly diffused from the patch, across the skin and into the bloodstream where it exerted its analgesic affect in the central nervous system. BuTrans was available at three different strengths (5, 10 and 20micrograms/hour) classified by how much dose was delivered each hour. BuTrans provided pain relief for up to seven days and was the only seven-day patch of its kind currently available. BuTrans was licensed for the 'treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia. BuTrans was not suitable for the treatment of acute pain' (BuTrans SPC) and its use was well established in the UK since launch in 2005.

Part 1: Panel rulings 1, 2 and the report to the Appeal Board

Napp noted that the Panel had ruled that the '… use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine.' and '… the analgesic efficacy of BuTrans in such patients could not be substantiated'. The case was reported to the Appeal Board because the '... Panel was concerned that the promotional material at issue was inappropriate .... Promoting a medicine in a patient group in whom there was no robust evidence of efficacy was an extremely serious matter'.

Napp submitted that in the context of the Panel's rulings it responded to ruling 1 and the reasons for the report to the Appeal Board together because there was significant overlap between both. Napp first responded to the reasons for the report to the Appeal Board and explained why it was appropriate to promote BuTrans for pain in dementia. The promotion of BuTrans for the treatment of pain in dementia was appropriate and not misleading.

Napp submitted that all three doses of BuTrans were licensed for 'the treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia'. Pain in patients who suffered from dementia represented a patient population with chronic pain and was therefore within the licensed indication. Dementia was a co-morbidity to chronic pain rather than dementia being a specific pain syndrome.

There was no difference in the pharmacological treatment of a patient suffering from chronic non-malignant pain whether they had dementia or not. Similarly, where dementia was a co-morbidity to other medical conditions, these conditions were still managed in the same way eg for patients with osteoporosis or pneumonia, bisphosphonates were used and appropriate antibiotics whether or not they had dementia.

Napp noted that the European Medicines Agency (EMA) had set out specific recommendations for pharmaceutical companies when developing new medicines for nociceptive pain (Committee for Proprietary Medicinal Products Guidance document for treatment of nociceptive pain 2009). In these regulatory guidelines there was no requirement to conduct specific pain in dementia studies and there was no specific pain in dementia indication. Further to this, the guidance stated that results could be extrapolated to elderly patients providing appropriate pharmacokinetic studies were conducted. In this regard, Napp had shown that no dose adjustments were required for BuTrans either in the elderly or in patients with renal impairment (BuTrans SPC). Dementia patients were often elderly and consequently suffered from significant renal impairment due to the ageing process. Therefore, in this context, BuTrans was a rational and sensible option to treat pain in this population. This was in contrast to the commonly prescribed opioids especially codeine, morphine and oxycodone, which were not recommended for chronic pain management of patients with severe renal impairment (Palliative Care Formulary, Twycross 2011).

Napp submitted that dementia patients felt pain in the same way as those without dementia (Kunz *et al* 2008) and that pain was under-recognised and undertreated in dementia patients (Horgas *et al* 1998 & Reynolds *et al* 2008). Further, clinicians, were bound by the General Medical Council's (GMC's) Duties of a Doctor, which specifically stated that they should 'take all possible steps to alleviate pain and distress whether or not a cure may be possible' (Good Medical Practice (GMP) Guidance 2013). The GMC also stated that 'You must take prompt action

if you think that patient safety, dignity or comfort is or may be seriously compromised' and that 'whether or not you have vulnerable adults or children and young people as patients, you should consider their needs and welfare and offer them help if you think their rights have been abused or denied' (GMP) Guidance 2013).

Napp stated that in the context of the wider literature, there was limited evidence for the treatment of pain using various analgesics in dementia because there was no difference in the pharmacological treatment of pain in a patient with or without dementia. This was reflected upon performing a comprehensive literature search as, aside from Husebo *et al*, its associated publications (Husebo *et al* 2011, Husebo *et al* 2014 and Sandvik *et al* 2014) and some earlier work which also investigated the effect of treating pain on behavioural outcomes (reviewed in Pieper *et al* 2013), there was only one trial in 39 patients that looked at effectiveness of an analgesic medicine for pain in patients with dementia (Buffum *et al* 2004).

Napp submitted that a health professional treating chronic pain in a dementia patient was faced with a number of clinical considerations to take into account. BuTrans made a rational choice for analgesia in this difficult-to-treat patient group because it provided consistent pain relief for up to seven days (BuTrans SPC). The convenience of a transdermal preparation that required changing every 7 days reduced administration time and staffing requirements in residential and nursing homes (Barber *et al* 2009). Napp noted that treatment compliance in dementia patients was challenging (Small *et al* 2007). However, patients on BuTrans showed greater treatment persistence vs codeine and tramadol over 6 and 12 months in over 4,900 patients of which 64% were older than 65 years (Gallagher *et al* 2009). Further, BuTrans offered an alternative method of administration in patients who had either difficulty swallowing or refused to swallow and the convenience of a weekly patch could ease the daily pill burden on patients (Conaghan *et al* 2011, Karlsson *et al* 2009). Napp again stated that although dementia patients were often elderly, BuTrans did not require dose adjustment in elderly patients or in those with severe renal impairment (BuTrans SPC). BuTrans was a viable alternative to codeine or tramadol as it was licensed for moderate pain and its dose equivalence range was within the licence range of codeine and tramadol's indication for pain (BuTrans SPC, codeine SPC and tramadol SPC) and the tolerability profile of BuTrans was comparable to that of other opioid analgesics including codeine and tramadol (Karlsson and Berggren 2008 and Conaghan *et al* 2011).

Napp had asked a university professor of ageing and geriatric medicine for his expert clinical opinion on this issue. He stated that 'clinically there is a constant emphasis that a diagnosis of dementia should not deny patients the same management as that afforded to those without a diagnosis of dementia. There is a very limited evidence base for the use of analgesia in older people. Therefore it is logical to use BuTrans in a stepwise approach to manage pain in the dementia population in the same way as would be the approach in patients without dementia.'

Napp noted that the Panel's ruling included comments regarding the adverse event profile of BuTrans including stating that 'confusion' was common in these patients (BuTrans SPC). Whilst this was important to be aware of, there was no contraindication or special warning against use in dementia within the BuTrans SPC.

Napp finally noted that despite being found in breach (ruling 2), the Panel in ruling 1 did not find Napp in breach with respect to the BMJ advertisement. The advertisement depicted a difficult-to-treat dementia patient suffering from pain, the Panel stated that 'it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'. This inferred the advertisement taken as whole, encompassing both the image and text, demonstrated a focus on pain and was not misleading with respect to the promotion of pain in dementia. Napp noted that the BuTrans pain in dementia sales-aid depicted the same patient as the advertisement in addition to further background on pain in dementia, why BuTrans 'makes sense' for managing pain in dementia and concluding 'See behavioural changes, check for pain, consider BuTrans'.

Napp submitted that with respect specifically to the pain in dementia webpage, taken as a whole encompassed only two pages (or 1.3%) of the BuTrans website totalling 150 pages, which was clearly focused on the management of pain.

In summary, Napp refuted the Panel's rulings and submitted that it was appropriate to promote BuTrans for the treatment of pain in dementia as this was within the licensed indication of the 'treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia'. There was no regulatory requirement to have specific pain in dementia data or indication. There was an ethical obligation to manage pain in patients who had dementia in the same way as managing pain in patients without dementia and clinically BuTrans made a highly rational option for the treatment of chronic pain in this difficult-to-treat patient group.

Part 2: Panel ruling 2a) Husebo

Napp noted that much of the debate centred on the Husebo study first published in the BMJ in 2011 (Husebo *et al* 2011) with post-hoc analysis published more recently (Husebo *et al* 2014 and Sandvik *et al* 2014).

Background

Napp submitted that the NICE Dementia Guidelines, (NICE CG42) the DoH (2009) Bannerjee Report on the use of antipsychotics in dementia patients and current guidelines from the Alzheimer's Society (2011) recommended that the first line management of behavioural and psychological disturbances (BPSD) in dementia should be a detailed assessment to identify any treatable causes. These included

delirium, depression and pain; such indicators for pain in a person with dementia included either withdrawn or disturbed behaviour.

Napp stated that failure to diagnose and treat causes of agitation and aggression in dementia patients had in part led to the over use of antipsychotics, which was associated with an increase in the number of cerebrovascular adverse events and deaths in dementia patients (Bannerjee 2009).

Napp submitted that a number of studies had confirmed the correlation between pain or discomfort and agitation in dementia patients (Pelletier and Landreville 2007, Ahn and Horgas 2013 and Zieber *et al* 2005). This had included a study of nursing home based dementia patients that demonstrated pain severity was positively linked to the frequency of agitated behaviours (Ahn and Horgas 2013).

Clinicians had the same ethical duty to manage pain in dementia as with patients who had pain without dementia. As previously outlined, in the GMC's GMP Guidance stated that doctors should 'take all possible steps to alleviate pain and distress whether or not a cure may be possible'.

Napp submitted that pain was both a clinical and subjective diagnosis, usually where the patient told you they were in pain. There were no clinical investigations that would confirm or refute the diagnosis. In dementia, patients were often verbally and cognitively impaired so struggled to communicate how they felt. This meant that the diagnosis of pain in a patient with dementia was more difficult to make than in a normal adult. It was often a diagnosis of exclusion (Royal College of Physicians, British Geriatrics Society and British Pain Society (RGP, BPS, BGS) Guidelines 2007) and clinicians should consider empirical analgesic trials or other pain-relieving interventions in patients who they thought were in pain might.

Context of the study

Napp submitted that based on the previous points the Husebo study was therefore a pragmatic investigation which recognised the established link between pain and agitation in patients with dementia and that behavioural disturbances played a critical role in the identification and management of pain in dementia. This pragmatic approach was fully in line with professional guidelines such as the RCP/BPS/BGS Guidelines which recognised that patients with dementia who were in pain might not complain of pain directly but might exhibit behavioural disturbances. Consequently Napp submitted that the Husebo study was conducted within the licensed indication for BuTrans.

Napp submitted that it clearly intended to demonstrate the impact that under-recognised pain had in dementia patients which was consistent with guidelines including the NICE dementia guidelines (NICE CG42), the DoH Bannerjee report and the Alzheimer's Society guidance 2011).

Napp submitted that with respect to Husebo *et al* (2011), it had clearly stated in both the webpage and sales aid that a step-wise approach to pain management was carried out (using various analgesics) and that BuTrans, which was licensed for moderate chronic pain, was a part of this approach. Napp did not claim that BuTrans directly improved agitation and aggression in dementia, nor did it claim that BuTrans alone was responsible for the observed finding. Therefore, Napp submitted that as suggested in the original complaint, the wording was indeed carefully chosen to reflect in the first instance that a step-wise approach to pain management was used, whilst secondly reflecting that BuTrans was part of (ie 'was associated with') the step-wise approach to the management of pain. However, Napp duly acknowledged that it could have explained Husebo *et al* (2011) in more detail surrounding those patients who were treated with BuTrans.

Beyond Husebo

Napp finally noted that Husebo *et al* (2011), referenced on the pain in dementia webpage, was only one of thirteen references which supported both the clinical background to pain in dementia and the rational use of BuTrans in the treatment of chronic non-cancer pain in this specific population. Many of these papers had already been cited in this response. This included the BuTrans SPC with licence information for clinicians and a Napp study which demonstrated BuTrans provided 7 day consistent efficacy (BuTrans SPC and Napp data on file BP98-0201). In addition Gallagher *et al* (2009) demonstrated patients on BuTrans showed greater treatment persistence vs codeine and tramadol. There were also four observational studies which demonstrated a high prevalence of pain in dementia patients in nursing homes (Zwakhalen *et al* 2009) and they returned similar pain scores as non-cognitively impaired patients (Closs *et al* 2004) but were prescribed less analgesics (Closs *et al* 2004 and Horgas and Tsai 1998). Further, there were three reviews on the under-treatment of pain in dementia (Cook *et al* 1999), the management of chronic pain in the elderly using transdermal buprenorphine including BuTrans (Vadivelu and Hines 2008) and a general review of BuTrans for treatment of pain (Plosker 2011). Finally, there was a DoH report on the overuse of antipsychotics in dementia (Bannerjee 2009) and an example of a local UK factsheet on pain in dementia (Sampson and Kitchen 2005).

In summary, Napp submitted that the Husebo study was a pragmatic investigation which recognised that behavioural disturbances played an important role in the identification and management of pain in dementia. The claims and substantiation for the use of BuTrans should also take into account the total literature base and not simply Husebo. Finally, for the reasons outlined previously the promotion of BuTrans for the treatment of pain in dementia was appropriate even without the Husebo study.

In the context of the above response, Napp therefore disagreed there had been a breach of Clauses 7.2 or 7.4.

Part 2: Panel ruling 2b)

'There was no evidence that treatment with BuTrans limited the unnecessary use of antipsychotics' and '... the statement was misleading by implication and could not be substantiated.'

Napp submitted that in its response it had outlined why it had not made a claim on antipsychotic usage and these key points still stood. In the context of the pain in dementia website Napp had not stated that BuTrans was associated with reduced antipsychotic usage, BuTrans was not mentioned in the sentence in order to distinguish it from the claim.

Napp submitted that to further substantiate this position, it was an established important clinical problem that antipsychotics were overused to treat behavioural and psychological disturbances (BPSD) in dementia including agitation and aggression. This overuse of antipsychotics was estimated to cause more than 1,620 cerebrovascular adverse events and more than 1,800 deaths per year (Bannerjee 2009). Napp submitted that it was therefore recommended that the first line management of BPSD should be a detailed assessment to identify any treatable causes, which included pain, before antipsychotics were even considered (Bannerjee 2009, NICE CG42, Alzheimer's Society Guidelines 2011). In this context Napp submitted that its intention was to raise awareness that 'effective management of pain can play an important part in the treatment of agitation and could reduce the number of unnecessary prescriptions for psychotropic drugs in this population' (Husebo *et al* 2011). Napp submitted that it had been careful not to mention BuTrans in the statement above, however it understood that there could be a perception by association but that was certainly not its intent.

Napp submitted that in the context of the above clinical guidance, it therefore did not agree there had been a breach of Clause 7.2 or 7.4.

Napp submitted that taking into consideration the reasons presented it considered that it was rational and clinically appropriate to promote BuTrans for the treatment of moderate chronic pain in dementia patients. As there was no difference in the pain pathophysiology there was no regulatory requirement to conduct specific clinical trials in this dementia patient population. Therefore, Napp did not agree that it had been misleading with regard to the evidence base and the licensed indication for BuTrans in the treatment of non-malignant pain of moderate intensity. In addition, Napp had also addressed the ruling with regards to claims for the analgesic efficacy of BuTrans in dementia patients. Napp included the Husebo paper as it was an important study which highlighted that proper step-wise pain management in this difficult to assess population could improve agitation and aggression. Napp contended that BuTrans was a sensible clinical choice for the treatment of moderate chronic pain in dementia patients not solely based upon the Husebo data but also by considering all of the literature quoted on the BuTrans pain in dementia webpage (thirteen references), within the advertisement (five references) and the sales aid (thirty references).

To conclude, Napp submitted that it took compliance very seriously and it felt strongly that the BuTrans pain in dementia campaign was appropriate given its response.

COMMENTS FROM THE COMPLAINANT

Antipsychotic reduction – the sales aid

The complainant noted that Napp had submitted that the webpage statement about antipsychotic use was a general statement which focussed on the potential reduction in the amount of antipsychotic prescriptions if pain was properly managed and that BuTrans itself was not claimed to cause reduction of antipsychotic use. The relevant text from the sales aid was:

> 'That's why once-weekly BuTrans patches are a sensible choice in dementia:
>
> - Can help improve pain-related behavioural changes as part of a pain management program, limiting unnecessary use of antipsychotics.'

The complainant alleged that the use of the word 'can' rather than 'may' meant that this went beyond a 'general statement' and suggested at least a subgroup (ie those with pain-related behavioural change) in whom antipsychotic use was limited.

Referencing

The complainant noted that Husebo *et al* (2011) was used as reference 11 to support the following four assertions:

1 'The limited ability of dementia patients to communicate effectively often leads to inappropriate use of antipsychotics before factors such as pain are explored[10,11]'.

The complainant had been unable to find this assertion anywhere in either reference. Reference 10 was to a comprehensive 62 page report on antipsychotic prescribing in dementia for the DoH (Bannerjee 2009). The only reference to pain in the report was as follows:

> 'The first line of management should be detailed assessment to identify any treatable cause of the BPSD (eg delirium, pain, depression); this should include taking the history of the problem, having the behaviour described by the carer/team, discussing current and past behaviour with the carer/team.'

2 'Effective management of pain can play an important part in the treatment of agitation and could reduce the number of unnecessary prescriptions for psychotropic drugs in this population[11]'.

The complainant alleged that this was actually a misquotation of the original which read: '... effective treatment approach for people with dementia and agitation, improved management of pain should also help to reduce the number of prescriptions for

anti**psychotics** in this population' (emphasis added by the complainant). The fact that the authors chose to dilute the message from the discussion of the academic paper suggested that they were entirely aware of the potential impact of claims concerning antipsychotic reduction.

3 'Effectively managing pain in dementia **can** help reduce behavioural disturbances limiting the unnecessary use of antipsychotics [10,11]' (emphasis added).

The complainant alleged that the 'can' here was stronger than statements in either reference. Husebo *et al* (2011) stated: 'The results also highlight the **potential** value of effective treatment of pain as a key part of reducing the use of antipsychotics and other psychotropic drugs in residents of nursing homes' and (as above) '... effective treatment approach for people with dementia and agitation, improved management of pain **sh**ould also help to reduce the number of prescriptions for antipsychotics in this population' (emphasis added).

4 'A step-wise approach to pain management, which included BuTrans was associated with reduced agitation, neuropsychiatric symptoms and pain compared with those receiving their usual treatment and care [11,12]'.

The complainant alleged that this was due to paracetamol not ***BuTrans***.

The complainant noted that reference 12 (Plosker 2011), was a comprehensive 18 page review about transdermal buprenorphine for pain. It was written by a staff author on the Adis review journal 'Drugs'. The single reference to 'dementia' in this 18 page review simply reprised the Husebo study as follows:

> 'Also noteworthy are results of a further randomized controlled trial, which suggest that transdermal buprenorphine, as part of a stepwise systematic approach to pain management in patients with concurrent dementia and chronic non-malignant pain, was associated with reduced agitation and overall neuropsychiatric symptoms, as well as improved pain relief, when compared with a control group receiving usual treatment and care.'

The complainant noted that this 'doubling up' in the referencing for this assertion in the sales aid (point 4 directly above), and also in Napp's response, was therefore misleading as it implied that a greater weight of evidence existed than was actually the case.

The complainant noted that reference 12 was also quoted in the sales aid as follows:

- 'BuTrans has a similar tolerability profile to that of other opioid analgesics[12].'

The relevant extracts from the section of the review on tolerability stated:

> 'In active-comparator clinical trials discussed in section 4, transdermal buprenorphine had a broadly similar tolerability profile to that of orally administered co-codamol[34] and prolonged release tramadol,[32] but was better tolerated than sublingually administered buprenorphine;[31] observed differences in the local tolerability profile reflect the different routes of administration. The most frequently reported adverse events with transdermal buprenorphine plus oral paracetamol versus oral co-codamol in patients with osteoarthritis were as follows: nausea (40% vs 25%), erythema at application site (27% vs 0%), constipation (26% vs 32%), pruritus at application site (17% vs 0%), dizziness (14% vs 6%) and vomiting (11% vs 8%).[34] In the comparative trial with tramadol, 14.5% of patients treated with buprenorphine and 29.2% of tramadol recipients withdrew from the study because of adverse events.[32]
>
> ... (with reference to placebo controlled trials) ....
>
> In a study in patients with osteoarthritis pain, 16.9% of all reported adverse events with transdermal buprenorphine 5–20 µg/h were deemed to be severe; the corresponding figure in the placebo group was 9.9%.[30] The most frequently reported adverse events with transdermal buprenorphine (n = 100) and placebo (n = 99) in the ITT population were gastrointestinal disorders (57% vs 25%), application site reactions (61% vs 40%) and CNS disorders (45% vs 18%). These were also the most common categories of adverse events in randomized, double-blind, placebo-controlled trials with transdermal buprenorphine in patients with chronic back pain,[36,37] and in a 6-month openlabel extension. [36].
> ...
>
> Older patients (≥65 years) had a higher incidence of constipation, dry mouth, diarrhoea, dizziness, fatigue and somnolence than patients aged <65 years, whereas headaches and application site reactions were reported more frequently in the younger cohort [52]'.

The complainant noted that reference 52 was to an abstract (Wen, Lynch, Munera *et al*, J Pain 2011) and he could not find further data on this point.

The complainant noted that the EMA note for guiding clinical investigation of medicinal products for treatment of nociceptive pain stated: '**As a rule** the results obtained in the general trial population can be extrapolated to the elderly patients provided appropriate pharmacokinetic studies are conducted' (emphasis added by the complainant). The Wen abstract suggested that, whatever the pharmacokinetic results indicated the elderly might break this rule.

A 'sensible choice'?

The complainant noted that in the sales aid, references 22-24 were used to support the assertion that:

> 'Butrans is a sensible choice ... that suits the challenges of dementia.[22-24].'

The complainant noted that reference 22, Priano *et al* (2006) was a wide ranging review of transdermal treatment of neurological disorders in the elderly. The complainant was unable to get a copy, but the advantages of patches was uncontentious.

The complainant noted that reference 24, Rinaldi *et al* (2005) reported an observational study of 419 outpatients with dementia (Mean Mini Mental State Examination (MMSE) =13). It reported that carer burden, distress, depression and anxiety were related to higher scores on behavioural disturbance and agitation in the patient. It did not refer to pain or any analysis relating to medication of any type. Whilst the complainant accepted that this pointed to a challenge of agitation in dementia, he/she alleged that it did not really support the idea that BuTrans was a sensible choice.

The complainant noted that reference 23, Manfredi *et al* (2003) seemed to be used to support the idea that opiates might have a role in managing agitation. The study was directed at agitation rather than pain. It did not use BuTrans. It found no effect on agitation of opiates. In this blinded, non-randomised, study patients were excluded if they were either sufficiently cognitively intact to be able to report pain reliably or if they had an 'obviously painful condition' which required active management. Despite these pain-related exclusion criteria, the median number of painful conditions was 5 (range 0-10). Mean MMSE=6. Inclusion criteria included persistent agitation for at least 3 months despite 2 psychotropics. Patients were all given 4 weeks of placebo then 4 weeks of an opioid (long acting oxycodone or, for those unable to swallow pills, long acting morphine). Of the 25 cases who completed 4 weeks of opiate, there was no difference in the primary outcome (agitation score) at the end. A further 11 cases dropped out in the placebo phase and 11 in the opiate phase. A *post hoc* analysis of 13 patients over the age of 85 years suggested that physical agitation was reduced.

The complainant thus alleged that references 23 and 24 did not support the claim that BuTrans was a 'sensible choice that suits the challenges in dementia'. Reference 23 was irrelevant and reference 24 did not have a sound statistical basis. To cite them in this way was misleading.

Clinical data cited in Napp's response

The complainant noted that in its appeal, Napp had referred to Buffum *et al* (2004) as the only other trial of pain relief in dementia. This double-blind, placebo controlled, crossover study of 39 patients with severe dementia who were not already on pain medication, showed that 650mg four times a day paracetamol had no effect on pain scores. The authors suggested that the results showed that paracetamol was 'inadequate for ... patients ... with significant discomfort'. However, the complainant alleged that there were two other possible explanations. Firstly, it was also possible that what was being measured was, in fact, agitation which had nothing to do with pain: in other words, analgesia was the wrong approach. There was a tautology linking pain or discomfort with agitation in dementia: the items assessed by scales used to measure 'discomfort' (such as the PAIN-AD, and its predecessor the DS-DAT which was used here) overlapped very substantially with scales used to measure 'agitation'. Secondly, it was also possible that staff in the care homes were good at distinguishing patients with genuine pain from those with agitation and had already started analgesia. 'Already on analgesia' was the reason for exclusion of 22% of potential participants.

With regard to the slides referred to by Napp the complainant noted that:

- Ahn and Horgas (2013) showed, in analysis of the minimum dataset (MDS2.0) scores of nursing home residents with dementia (N=56,577), a 4% increase in risk of aggression in patients with pain (95%CI OR=1.01-1.08) and a 17% increase in agitation (95CI OR=1.13-1.20).

- Pelletier and Landreville (2007) found no relationship between 'aggressive behaviour' and discomfort in 49 nursing home residents. In contrast, discomfort accounted for 30% of the variance in 'verbally agitated behaviour' which comprised 'complaining, constant requests for attention, negativism, repetitious sentences or questions, screaming.

- Vadivelu and Hines (2008) (cited in the BMJ advertisement) reviewed transdermal buprenorphine in the elderly and the only (unreferenced) mention of dementia was 'transdermal buprenorphine will be a useful tool for the administration of drugs (sic) when patients are forgetful, or are unable to swallow oral medications'.

- Pieper (2013) (cited in the BMJ advertisement) was a systematic review of either a) interventions targeting pain with or without behavioural disturbance, or b) pain interventions targeting behaviour.

Pharmacological studies

The complainant noted that the 6 included studies of the pharmacological treatment of pain in dementia included Husebo *et al* (2011), Buffum *et al* (2004) and Manfredi *et al* (2003) (discussed above). Passmore (2011) was a case report of successful treatment of a 104 year old man with sublingual sufentanil. Elliott (2009) reported an ABAB (no intervention baseline (A1), and intervention phase (B1), with each phase repeated (A2 and B2)) withdrawal of paracetamol from 3 patients which showed reduced guarding, grimacing and vocalisations when on paracetamol. In Chibnall (2005) 25 patients were randomly assigned to paracetamol or placebo. The complainant noted that there was no effect on agitation.

Complex interventions

The complainant alleged that of the 9 included studies identified as targeting 'both pain and behaviour' in dementia, only 2 were relevant because they allowed inclusion of analgesia

interventions. Kovach (2006) was rated as the best quality randomised controlled trial. This was a trial in 114 people of a complex intervention of 4 weeks of stepped care. It showed benefit on 'discomfort' but not on behaviour. Analgesia, which was step 4 of 5, was prescribed to 26 of 57 in the interventions arm. Whilst it was effective in 15/20 cases, the prescription was for a 'narcotic' in only 5 cases. No further details were available. Chapman and Toseland (2007) was a 2x2 partial cross over trial of advanced illness care teams which was effective in reducing pain and agitated behaviour. This was published in the Journal Social Work and the complainant had not been able to get a copy.

In summary, the complainant alleged that the best evidence was that pain in dementia increased the odds of aggression by 4%. There was no evidence that opiates were of any benefit in dementia.

The complainant alleged that the citations in the promotional material were misleading because they implied that there was an evidence base to support the clinical approach of: 'See behavioural changes, check for pain, consider BuTrans in dementia'.

Ethical and GMC obligations

The complainant noted Napp's contention that the ethical obligation for the clinician here was clear. One should treat pain where one saw it. Pain was certainly worth considering when faced with an agitated patient with dementia.

The complainant noted that there were no trials registered for buprenorphine and dementia on Clinicaltrials.gov or the International Standard Randomised Controlled Trial Number register, suggesting that Napp had no imminent plans to improve the quality of the evidence base to support the marketing of its product for this population.

In summary, the complainant noted that conducting trials in patients with dementia was difficult, and trials in dementia patients with agitation were amongst the most challenging in medicine. Husebo and her colleagues had done a good job in advancing this field but had not produced evidence of any benefit for BuTrans. It was unfortunate therefore that this trial appeared to have been the main stimulus for Napp's promotional campaign.

The complainant stated that patients with dementia – some of whom complained, were negative and constantly requested attention – had been subjected to over-prescription of almost all classes of psychoactive medication: benzodiazepines then antipsychotics. When it was not only asserted that agitation was a sign of pain which could not be otherwise expressed, but also pain scales included items which were agitated behaviours, then clinicians were likely to be drawn into an irrefutable tautology. When combined with powerfully emotive promotion of a treatment for the agitation/pain, this was a sure route to over-treatment.

The complainant alleged that in the context of the current evidence, this promotional campaign unduly emphasised dementia as a population for treatment with BuTrans, was ambiguous as to whether it promoted BuTrans for pain or agitation, misled in its implication that BuTrans 'could' reduce antipsychotic prescribing, did not present or refer to sufficient material to allow recipients to form an opinion of its value, and used references to studies in ways which were misleading and did not have a sound statistical basis.

APPEAL BOARD RULING

The Appeal Board accepted that correctly diagnosing pain in dementia patients posed particular problems for the prescriber, the patient and their carers. Dementia patients were a vulnerable group.

The Appeal Board considered that the over-riding message of the material at issue, which included the claim 'BuTrans makes sense in dementia', was that pain was a major cause of agitation in dementia patients who could not otherwise express their pain and so a sensible choice was to prescribe BuTrans to treat such pain. The material at issue had oversimplified the treatment pathway for pain in dementia. The World Health Organisation (WHO) pain relief ladder referred to the stepwise treatment of pain. The Appeal Board noted that the website and detail aid had each referred to a '… step-wise approach …', however not until the last bullet on page 1 of the website and on page five of the detail aid. In the Appeal Board's view, the material at issue should have referred to the various steps in a stepwise treatment plan at the outset, including alternative treatments and precautions that needed to be considered before a prescriber could responsibly prescribe BuTrans for pain in dementia patients. In that regard the Appeal Board queried whether sufficient emphasis had been given to the side-effect profile of BuTrans, which included, *inter alia*, confusion as common, agitation and anxiety as uncommon and psychotic disorder as rare especially as dementia patients would be unlikely to be able to report, and prescribers and carers would be unlikely to recognise, such side effects which might appear to be part of the patient's underlying symptoms of dementia.

The Appeal Board noted that the only clinical data concerning the use of BuTrans in the treatment of pain in dementia was Husebo *et al* (2011). The primary outcome measure was agitation as assessed by a nurses' rating questionnaire. Assessment of pain using the observational MOBID-2 pain scale was a secondary outcome measure. A further analysis of the study results published after the material at issue had been approved showed that the treatment effect of BuTrans was not apparent until week eight of the eight week study. The 39 BuTrans patients in the study had not been positively diagnosed with non-malignant pain of moderate intensity such that they required an opioid, nor was it clear that they did not have acute pain. The Appeal Board noted the Panel's concerns about the study and Napp's response to these points in its appeal. The Appeal Board noted from the Napp representatives at the appeal that Husebo *et al* (2011) was not powered to measure the effect of BuTrans on pain in patients

with dementia. The Appeal Board considered that Husebo *et al* (2011) was not sufficiently robust to support the claims about the use of BuTrans in the treatment of pain in patients with dementia.

The Appeal Board thus considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and claims for analgesic efficacy in such patients could not be substantiated. The Appeal Board noted that treating dementia patients in pain with BuTrans was not inconsistent with its licensed indication as long as those patients had non-malignant pain of moderate intensity such that an opioid was necessary for obtaining adequate analgesia. However, to have a campaign which actively promoted its use based on data in a sub-group for whom there was no robust analgesic evidence was of concern. The Appeal Board was particularly concerned about the safety of using BuTrans in this vulnerable patient group given that if they did not have the verbal skills to express and communicate pain then they were also unlikely to be able to express and communicate side-effects such as confusion and anxiety etc. The Appeal Board thus upheld the Panel's ruling of a breach of Clauses 7.2 and 7.4. Napp's appeal on this point was unsuccessful.

The Appeal Board noted that the claim on the website 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics.' appeared below the heading 'BuTrans makes sense in dementia'. A similar claim appeared on pages five and eight of the detail aid which was headed 'BuTrans is a sensible choice …'. The Appeal Board considered that in the context in which they appeared, these claims could only be referring to the effect of BuTrans. The Appeal Board considered that Napp had not provided evidence to show that the use of BuTrans limited unnecessary use of antipsychotics. The Appeal Board thus upheld the Panel's ruling of a breach of Clauses 7.2 and 7.4. Napp's appeal on this point was unsuccessful.

With regard to the advertisement, the Appeal Board considered that given the strap line 'Dementia hurts enough without pain' it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients and not for the treatment of agitation. On this narrow allegation the Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The complainant's appeal on this point was unsuccessful.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted its concerns and rulings above and that the Panel had required the material to be suspended pending the final outcome of the case. Given its rulings of breaches, the Appeal Board noted that the material at issue would now have to be withdrawn. The Appeal Board decided, in this instance, to take no further action in relation to the report from the Panel.

Complaint received **23 July 2014**

Case completed **7 November 2014**

CASE AUTH/2724/7/14

TILLOTTS v FERRING

Pentasa cost comparison chart

Tillotts complained about a cost comparison bar chart for Pentasa (mesalazine) entitled 'Pentasa is less expensive than many other brands of 5-ASA'; the chart was a 'Comparison based on annual drug cost of commonly prescribed oral mesalazine preparations at their licensed dosage(s) for the maintenance of remission of mild to moderate UC [ulcerative colitis]'. The other mesalazine products featured in the chart were, *inter alia*, Octasa marketed by Tillotts.

Tillotts alleged that the bar chart implied that Pentasa was the cheapest oral mesalazine for the maintenance treatment of mild to moderate ulcerative colitis (UC). The chart cited daily Pentasa doses of 1.5g and 2g/day, whereas the summary of product characteristics (SPC) stated 'Maintenance treatment: Individual dosage. Recommended dosage, 2g mesalazine once daily'. Tillotts alleged that the 1.5g/day dose was inconsistent with the marketing authorization and that the chart was misleading, unfair and misrepresented the cost of Pentasa. The inappropriate use of the 1.5g/day dose for Pentasa was reinforced by the fact that the daily doses of the comparator products were precisely those stated in the relevant SPCs.

The detailed response from Ferring is given below.

The Panel noted that the bar chart compared the annual medicine acquisition cost of 'commonly prescribed oral mesalazine preparations at their licenced dosage(s) for the maintenance of remission of mild to moderate UC'. The doses cited for Pentasa were 1.5g/day and 2g/day at an annual cost of £336.62 and £448.83 respectively. The Pentasa SPC stated that for the maintenance of remission in UC, the dose of Pentasa could be individualised and that the recommended dose was 2g once daily. The Panel noted the submission that according to 2013 prescription data a small minority of Pentasa maintenance prescriptions were written for 1.5g/day. The Panel noted the reference to individual doses in the SPC and considered that whilst some patients might be maintained on 1.5g/day and some on the recommended dose of 2g/day, some patients might be prescribed more than 2g/day.

The Panel noted that the doses (and costs) shown for comparator products were the lowest and highest maintenance doses as stated in their respective SPCs.

The Panel noted its comments above and considered that the doses and costs shown for Pentasa were not wholly comparable with the doses and costs shown for the other mesalazine preparations. Supplementary information to the Code stated, *inter alia*, that valid comparisons could only be made where like was compared with like. In the Panel's view the cost comparison chart at issue had not compared like with like. The doses and costs shown for Pentasa had been derived from prescription data, clinical trials, treatment guidelines and the SPC. The apparent weight given to the use of Pentasa 1.5g/day was the same as that given to the use of the recommended dose of 2g/day which was the only maintenance dose to be specifically quantified in the Pentasa SPC. The doses and costs shown for the other medicines were derived only from the range of doses specifically quantified in their respective SPCs. The Panel thus considered that the impression given in the cost comparison of the status of the 1.5g/day dose, compared with the status of all of the other doses stated was misleading as alleged and a breach of the Code was ruled.

The Panel noted that the cost comparison chart had referred to a maintenance dose of 1.5g/day for Pentasa. Although the Pentasa SPC stated that the recommended maintenance dose was 2g/day, it also referred to 'Individual dosage'. The Panel noted that clinical guidelines referred to the use of at least 1.2g/day mesalazine for maintenance therapy in UC and clinical studies had shown the benefit of Pentasa 1.5g/day in the maintenance treatment of UC. The Panel noted that although 1.5g/day was not cited in the Pentasa SPC for maintenance therapy, given the reference to individual dosing, it was not inconsistent with the particulars listed in the SPC. No breach of the Code was ruled.

Tillotts Pharma UK Limited complained about a cost comparison bar chart for Pentasa (mesalazine (5-amino-salicylic acid (5-ASA))) which was included in an e-detail aid (ref PA/283/2014/UK) produced by Ferring Pharmaceuticals Ltd. The chart was entitled 'Pentasa is less expensive than many other brands of 5-ASA' and beneath it was explained that the chart was a 'Comparison based on annual drug cost of commonly prescribed oral mesalazine preparations at their licensed dosage(s) for the maintenance of remission of mild to moderate UC [ulcerative colitis]'. The other mesalazine products featured in the chart were Octasa (marketed by Tillotts), Asacol, Mezavant and Salofalk. The annual cost or range of the costs of various doses was given. The doses ranged from 1.2g/day (Octasa) to 3g/day (Salofalk sachets).

Pentasa was indicated for the treatment of mild to moderate UC and for the maintenance of remission of UC. Section 4.2 of the Pentasa summary of product characteristics (SPC) stated that the dose for maintenance treatment was 'Individual dosage. Recommended dosage, 2g mesalazine once daily'.

COMPLAINT

Tillotts explained that the material in question was a slide which presented a chart of annual costs for various oral mesalazine preparations used for the maintenance treatment of UC. The bar chart was

headed 'Pentasa is less expensive than many other brands of 5-ASA' and included annual costs of a range of mesalazine products, including Octasa 400mg and 800mg tablets. Tillotts alleged that the bar chart implied that Pentasa was the cheapest oral mesalazine for the maintenance treatment of mild to moderate UC.

Tillotts alleged that one of the daily doses of Pentasa used for comparison purposes was not supported in the posology section (Section 4.2) of the Pentasa SPC. The chart cited daily doses of 1.5g and 2g per day for Pentasa, whereas the SPC stated 'Maintenance treatment: Individual dosage. Recommended dosage, 2g mesalazine once daily'. Tillotts alleged that the chart was deliberately misleading and that it was not appropriate to base cost comparisons on doses which were not specifically stated in the SPC. Tillotts alleged that the chart misrepresented the cost of Pentasa and presented an unfair comparison.

The inappropriate use of the 1.5g/day dose for Pentasa was reinforced by the fact that the daily doses of the comparator products cited in the chart were precisely those stated in the relevant SPCs. In the case of Octasa 400mg and 800mg, maintenance treatment was possible within a range of recommended doses ie 1.2g to 2.4g per day. The bar chart in question made that clear and provided a range of annual medicine costs at the minimum and maximum doses. However, the range of doses depicted for Pentasa was inconsistent with the product's SPC.

The only dose at which Pentasa and Octasa might be directly compared was 2g/day, due to the differences in available tablet strengths. At such a dose, Pentasa was more expensive than Octasa (£448.83 vs £395.42 respectively), rendering false the claim that Pentasa was less expensive. During inter-company dialogue, Ferring contended that 1.5g/day was a commonly used dose and stated in written correspondence that 1.5g/day was the 'minimum daily dose' for Pentasa.

Tillotts alleged a breach of Clause 3.2 in that a dose cited for Pentasa was not supported by the Pentasa SPC and was thus inconsistent with the marketing authorization, and a breach of Clause 7.2 in that the comparison was misleading and unfair.

RESPONSE

Ferring submitted that the bar chart was an accurate, balanced and fair comparison of the acquisition costs of various mesalazine formulations available for the maintenance of remission in UC; it was not designed to imply that Pentasa was the cheapest choice. The chart was clear and showed that Salofalk was the cheapest brand in terms of annual medicine costs of commonly prescribed oral mesalazine preparations for the maintenance of remission of mild to moderate UC.

Ferring denied that the calculations used to derive the comparative annual cost of the various mesalazine products were misleading. The chart demonstrated the dosage range costs for various brands of mesalazine and took into account the respective SPCs, the available drug formulations (Monthly Index of Medical Specialities (MIMS), June-August 2014) and the British Society of Gastroenterology (Mowat *et al* 2011) and European Crohn's and Colitis Organisation recommendations (Dignass *et al* 2012).

Due to the different quantitative composition of the products, a 'direct dose-by-dose comparison' could not be made. The doses and respective annual costs shown in the chart were based on the information provided in MIMS, June-August 2014 and Ferring provided details of the calculations used.

Ferring denied that the chart was inconsistent with the Pentasa SPC. The Pentasa SPCs for 500mg tablet, 1g tablet, 1g sachet and 2g sachet all stated: 'for maintenance treatment: Individual dosage. Recommended dosage, 2g mesalazine once daily'.

Although 2g per day was the recommended dose, other individualised doses could be used within the product licence, as stated in the SPC. The 1.5g/day dose was commonly used based on the following:

a) The 1.5g dose was consistent with the British Society of Gastroenterology guidelines (Mowat at al) recommending oral mesalazine 1.2-2.4g daily for maintenance of remission in UC.
b) The European Crohn´s and Colitis Organisation guidelines stated that the minimum effective dose of oral 5-aminosalicylic acid was 1.2g per day for maintenance of remission in UC (Dignass *et al*).
c) The 1.5g dose has been shown to be an effective dose in clinical trials (Fockens *et al* 1995, Mulder *et al* 1988 and Munakata *et al* 1995).
d) UK patients were currently prescribed the 1.5g/day maintenance dose of Pentasa (Ferring Data on File). Prescription data showed that, in 2013, 18,873 prescriptions were issued where the 1.5g/day dose of Pentasa 500mg tablets was prescribed as either 1 tablet 3 times a day, or 3 tablets once a day. This represented 7.1% of all 500mg Pentasa tablet prescriptions or 6.1% of all Pentasa tablets prescribed (1g and 500mg). In addition, an analysis of co-prescribed medicines showed that in 2013 there were 1,025 co-prescribed prescriptions for Pentasa (711 prescriptions for 500mg Pentasa tablet where a 1g Pentasa tablet was co-prescribed and 314 prescriptions for 1g Pentasa tablet where a 500mg Pentasa tablet was co-prescribed).

As Pentasa was not available in a tablet strength that could be administered as 1.2g, which was the minimum dose recommended by the British Society of Gastroenterology and the European Crohn's and Colitis Organisation for maintenance treatment of ulcerative colitis, Ferring submitted that it was justifiable to use the 1.5g/day dose as the low prescribed dose for cost demonstration.

Ferring submitted that as stated above, the aim of the cost comparison bar chart was to demonstrate the range of annual medicine acquisition costs of commonly prescribed mesalazine formulations available for the maintenance treatment of remission in UC.

Ferring denied a breach of Clause 3.2 as the cited dose of 1.5g Pentasa was consistent with its marketing authorization as noted above. Ferring also denied a breach of Clause 7.2 as the material was not misleading and represented an accurate, balanced, fair, objective and unambiguous comparison of the acquisition costs of commonly prescribed mesalazine formulations available for maintenance of remission in UC as explained above.

PANEL RULING

The Panel noted that the bar chart compared the annual medicine acquisition cost of 'commonly prescribed oral mesalazine preparations at their licenced dosage(s) for the maintenance of remission of mild to moderate UC'. The doses cited for Pentasa were 1.5g/day and 2g/day at an annual cost of £336.62 and £448.83 respectively. The Pentasa SPC stated that for the maintenance of remission in UC, the dose of Pentasa could be individualised and that the recommended dose was 2g once daily. The Panel noted the submission that according to 2013 prescription data some patients were prescribed 1.5g/day Pentasa which was assumed to be for maintenance treatment given that the dose for acute treatment was likely to be larger (the SPC referred to an individual dosage of up to 4g mesalazine per day). It appeared from the data submitted by Ferring that only a small minority of Pentasa prescriptions were written for 1.5g/day (either as 3 x 500mg or 1 x 500mg + 1 x 1g). The Panel noted the reference to individual doses in the SPC and considered that whilst some patients might be maintained on 1.5g/day and some on the recommended dose of 2g/day, some patients might be prescribed more than 2g/day.

The Panel noted that the doses (and costs) shown in the chart for the other mesalazine preparations were the lowest and highest maintenance doses as stated in their respective SPCs. Thus the dose stated in the Octasa MR tablets 400mg SPC for maintenance therapy was three to six tablets a day in divided doses and so the two doses shown in the bar chart were three tablets a day (1.2g, £237.25) and six tablets a day (2.4g/day, £474.50). Comparable data was given for Octasa MR 800mg tablets, Asacol 400mg and 800mg tablets, Mezavant XL tablets, Salofalk 500mg tablets and Salofalk 3g sachets. The Panel thus noted that no maintenance dose other than that specifically quantified in the SPC was shown for any of the mesalazine preparations apart from Pentasa.

The Panel noted its comments above and considered that the doses and costs shown for Pentasa were not wholly comparable with the doses and costs shown for the other mesalazine preparations. The supplementary information to Clause 7.2, price comparisons, stated that as with any other comparison, price comparisons must be accurate and fair and must not mislead. Valid comparisons could only be made where like was compared with like. In the Panel's view the cost comparison chart at issue had not compared like with like. The doses and costs shown for Pentasa had been derived from prescription data, clinical trials, treatment guidelines and the SPC. The apparent weight given to the use of Pentasa 1.5g/day was the same as that given to the use of the recommended dose of 2g/day which was the only maintenance dose to be specifically quantified in the Pentasa SPC. The doses and costs shown for the other medicines had been derived only from the range of doses specifically quantified in the respective SPCs. The Panel thus considered that the impression given in the cost comparison of the status of the 1.5g/day dose, compared with the status of all of the other doses stated was misleading as alleged and a breach of Clause 7.2 was ruled.

The Panel noted that the cost comparison chart had referred to a maintenance dose of 1.5g/day for Pentasa. Although the Pentasa SPC stated that the recommended maintenance dose was 2g/day, it also referred to 'Individual dosage'. The Panel noted that clinical guidelines (Mowat *et al* and Dignass *et al*) referred to the use of at least 1.2g/day mesalazine for maintenance therapy in UC and clinical studies (Fockens *et al* and Mulder *et al*) had shown the benefit of Pentasa 1.5g/day in the maintenance treatment of UC. The Panel noted that although 1.5g/day was not cited in the Pentasa SPC for maintenance therapy, given the reference to individual dosing, it was not inconsistent with the particulars listed in the SPC. No breach of Clause 3.2 was ruled.

Complaint received **30 July 2014**

Case completed **9 September 2014**

MEMBER OF THE PUBLIC v ROCHE

Newspaper article about Avastin

An anonymous, contactable member of the public complained about an article entitled 'Young cancer patient forced to pay £2,000 a week for treatment drugs – after NHS refuses' which appeared in the Daily Mirror newspaper and in the Mirror online. The article referred to Avastin (bevacizumab) which was marketed by Roche and indicated in combination for the treatment of certain cancers. The complainant submitted that he/she was technically whistleblowing but had to do so anonymously because of fear of internal recriminations.

The complainant stated that it was clear that the article had been company-inspired and placed in the newspaper by Roche's agents. The article was extremely well informed and referred to highly technical issues such as the National Institute for Health and Care Excellence (NICE), overseas use of Avastin and clinical data. The story focused on the use of Avastin to treat a brain tumour when the medicine was not licensed for such use. The complainant stated that this was a very serious breach of the Code as it was off-label promotion of a medicine and to a lay audience. The article inferred that the medicine extended and improved quality of life when there was no data to prove this.

The complainant stated that he/she knew that the article was promoted by Roche through its public relations agents. The complainant alleged that Roche and its agents contacted the journalists concerned after getting a tip about the patient from the sales force. The complainant stated that the content of the article was agreed by Roche; any suggestion to the contrary would be revealed as false by the paper trail with Roche, its agent and the Daily Mirror.

The detailed response from Roche is given below.

The Panel noted that the complainant had provided little information and no documentation to support his/her complaint despite reference to a paper trail between Roche and its agents. A request for further information had gone unanswered. As with any complaint, the complainant had to prove his/her complaint on the balance of probabilities; the matter would be judged on the evidence provided by the parties.

The parties' accounts differed. The complainant alleged that Roche was involved with the newspaper story; Roche denied that this was so. The company was aware of the story in a local newspaper before it received the enquiry from the journalist. Although the company had interacted with the journalist, it had stated in writing that Avastin was not licensed in the UK for the treatment of brain tumours and in response to a query had verbally told him/her that the medicine was so licensed in Japan. The company submitted that it had not tipped the newspaper off about the patient at issue. Roche provided written statements from its agents each stating that they had not been involved in the generation of the story.

The Panel considered that on the basis of the evidence provided by the parties, the complainant had not proven that, on the balance of probabilities, Roche or its agents had instigated or placed the newspaper article as alleged. No breaches of the Code were ruled including Clause 2.

An anonymous but contactable member of the public complained about an article entitled 'Young cancer patient forced to pay £2,000 a week for treatment drugs – after NHS refuses' which appeared in the Daily Mirror newspaper and in the Mirror online. The medicine which the patient had to fund was Avastin (bevacizumab) marketed by Roche Products Limited. Avastin was indicated, in combination with another therapy, for the treatment of certain cancers.

COMPLAINT

The complainant stated that it was clear that the article had been company-inspired and alleged that it breached the Code in several important ways and was placed in the newspaper by Roche's agents. The article was extremely well informed and included references to highly technical issues such as the National Institute for Health and Care Excellence (NICE), overseas use of Avastin and clinical data.

The complainant stated that because of his/her job (and he/she could not disclose this for fear of dismissal), he/she knew that the article was promoted by Roche through its public relations agents and that this was in breach, *inter alia*, of the Code. The complainant submitted that he/she was technically whistleblowing but had to do so anonymously because of fear of internal recriminations such was the climate of fear in the organisation.

The complainant alleged that the article fundamentally breached the Code in that:

1 Roche and its agents initiated the article by contacting the journalists concerned after getting a tip about this patient from the sales force. There would be records of these discussions that must be disclosed. The contents of the article and the specifics below were agreed by Roche and its agents with the journalists so any suggestion from Roche that this was nothing to do with it would be revealed as false by the paper trail with Roche, its agents and the Daily Mirror.

2 The article was in mainstream media and this was deliberately selected by Roche's agent at its request. Under the Code the pharmaceutical

company was responsible regardless of who pursued the activity.

3 The article promoted a brand name of a medicine to non-prescribers.

4 The story focused on the use of Avastin to treat a brain tumour when the medicine was not licensed for such use. This was off-label promotion of a medicine and to a lay audience.

5 The article inferred that the medicine extended and improved quality of life when there was no data to prove this.

6 The article referred to use in other countries without any explanation.

The complainant stated that he/she was very worried about the ethical behaviour of the company he/she worked for.

In response to a request for further information, the complainant did not reply.

When writing to Roche, the Authority asked it to respond in relation to Clauses 2, 9.1, 23.1 and 23.2 of the Code.

RESPONSE

Roche explained that Avastin was licensed for the treatment of numerous advanced solid tumour cancers; it was, however, not licensed in the European Union (EU) for glioblastoma (GBM) and it was completely counter to Roche UK's strategy to promote Avastin for GBM or any other unlicensed indication.

Roche's named public affairs agency provided cross-portfolio advice and supported Roche with respect to healthcare policy. The public affairs agency was not retained by Roche to provide any public relations or public affairs activities in respect of Avastin or any other specific Roche product. Specifically, Roche did not instruct the agency to act on its behalf in respect of the newspaper article in question.

Roche's named marketing and public relations agency provided support for the Avastin brand to the public relations team. Specifically, Roche did not instruct this agency to act on its behalf in relation to placing the Daily Mirror article, although it did instruct it to help prepare the reactive statement referred to below.

Roche explained that its global media relations team received an enquiry on Monday, 28 July, from a journalist, who stated that he/she was preparing a national story about a man with an inoperable brain tumour. Roche was asked to 'send across a statement asap (within the next few hours) detailing countries where Avastin is used as a treatment for this form of cancer and more details on the drug. Any details on successful trials of treatment as well as any reaction to this case'. Roche outlined the timeline of associated event:

On 17 July 2014, Roche was notified by a media monitoring company that a story had appeared in a local newspaper about a named individual, whose family was fundraising to support his treatment. Avastin was mentioned within the article.

On 28 July 2014, a media enquiry was received by Roche global media relations team (in Basel, Switzerland) and passed to the UK public relations team. Roche initiated the creation of a written reactive statement to the story in conjunction with its marketing and public relations agency. Roche did not instruct its public affairs agency in relation to this response. The reactive statement was raised and reviewed within Roche's approval system. Roche telephoned the journalist and asked for clarification as to whether the patient had GBM. The journalist responded that he did. Roche responded verbally and stated that Avastin was not licensed for GBM. In response to the journalist's query regarding where Avastin was licensed in other countries for GBM, Roche stated that Avastin was licensed for GBM in Japan. Later that day the online version of the story was published.

On 29 July 2014, the Daily Mirror published the story in print.

On 31 July 2014, the reactive statement was signed-off by two final signatories in line with Roche's standard operating procedures.

Roche submitted that healthcare compliance and human resources led an internal investigation; they interviewed appropriate Roche UK head office, field medical staff and field sales staff, searched Roche's customer relationship management (CRM) systems for applicable entries by both field medical staff and field sales staff, reviewed emails sent/received by relevant field, marketing and communications staff and reviewed information provided by medical information in response to enquiries. This very thorough investigation, including the review of several thousand emails, failed to find anything to suggest that anyone at Roche contacted the Daily Mirror directly or indirectly (other than the reactive contact with the journalist referred to above), or provided any form of tip about the patient.

Roche also interviewed both its public affairs and marketing and public relations agencies. Both confirmed that they had had no involvement in the story and that they were not instructed by Roche to place the story.

Roche noted that it had also contacted the Daily Mirror which responded that its policy was to not reveal its sources for any article it published.

In conclusion, Roche submitted that its thorough investigation had found no evidence to support the complainant's allegations that Roche facilitated the interview with the patient in any way or that it was involved with the placement of the article in the Daily Mirror. Roche denied breaches of Clauses 2, 9.1, 23.1 and 23.2.

In response to a request for more information, Roche confirmed that its global team had had no

involvement with either the journalist or with the enquiry other than its handling of the initial enquiry as stated above.

PANEL RULING

The Panel noted that the complainant had provided little information and no documentation to support his/her complaint despite reference to a paper trail between Roche, and two named agents. Although the anonymous complainant had provided email contact details, a request for further information had gone unanswered. As with any complaint, the complainant had the burden of proving his/her complaint on the balance of probabilities; the matter would be judged on the evidence provided by the parties.

The Panel noted that the parties' accounts differed. The complainant had alleged that Roche was involved, directly or indirectly, with the story that had appeared in the Daily Mirror. Roche, following its investigation of the matter, denied that this was the case. The company was aware of the story in the local newspaper before it received the enquiry from the journalist. Although the company had interacted with the journalist as a result of his enquiry, it had stated in writing that Avastin was not licensed in the UK for the treatment of brain tumours and submitted that in a verbal response to the journalist it had stated that the medicine was so licensed in Japan. The company submitted that it had not provided the newspaper with a tip off about the patient at issue. Roche provided written statements from both its named agents each stating that they had not been involved in the generation of the Daily Mirror story.

The Panel considered that on the basis of the evidence provided by the parties, the complainant had not proven that, on the balance of probabilities, Roche or agents working on its behalf had instigated or placed the Daily Mirror article as alleged. No breaches of Clauses 2, 9.1, 23.1 and 23.2 were ruled.

Complaint received **30 July 2014**

Case completed **15 October 2014**

CASE AUTH/2727/8/14

PHARMACIST v PIERRE FABRE

Promotion of Navelbine

A pharmacist complained about a letter sent by Pierre Fabre regarding Navelbine (vinorelbine) oral dosing to oncology pharmacists.

Navelbine was licensed as a single agent or in combination for the first line treatment of stage 3 or 4 non small cell lung cancer (NSCLC) and the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The letter was headed 'Under-dosing of Navelbine Oral' and stated that the only recommended dose of single agent Navelbine in advanced breast cancer was 80mg/m^2 weekly (following three doses at 60mg/m^2). The letter stated that efficacy was clearly associated with appropriate dosing and explained the consequences of under-dosing. It encouraged checks of local protocols to ensure that Navelbine oral was being used at the appropriate dose and included a bar chart.

The complainant referred in detail to missing information and noted that no prescribing information was provided.

The complainant pointed out that the indication in the letter was simply listed as 'Advanced Breast Cancer' rather than the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The complainant stated that the dosage information in the letter, which was the key point of the letter, did not reflect a number of exclusions to dose escalation in the summary of product characteristics (SPC) related to full blood count. The letter stated that 'a blood test' was required for each dose when increasing frequency of dose but did not specify which tests were needed and did not highlight that that blood tests would define if dose escalation was appropriate.

The complainant noted that the approved name appeared directly below the most prominent display of the brand name, it did not appear with the same area as the brand name. There was no statement regarding reporting adverse events.

The complainant alleged that while the statement 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefit for patients' should have been accompanied by an evidence base relevant to the use of anti-cancer agents in Stage 3 or 4 breast cancer, where the primary treatment objective was not always survival. The complainant was aware of very little evidence to substantiate the statement in this setting and none for vinorelbine dosing.

The complainant stated that the graph included in the letter used an example dose for a 1.7m^2 patient and while that was an appropriate example the need to round to available capsule sizes meant that some adjustment of final dose given occurred. It was hard to be convinced that those values were not selected to make the difference as numerically large as possible.

The complainant alleged that there had been an attempt to make the communication appear like a safety letter rather than promotional material. A clinician following the advice would use 50% more of the medicine and the complainant could not see how this had not resulted in promotion.

The complainant used the SPC schedule but frequently did not dose escalate due to full blood count or due to other toxicity/response profiles. The complainant was concerned that clinicians would half read the letter and feel they should be dose escalating rather than optimising patient benefit with toxicity.

The detailed response from Pierre Fabre is given below.

The Panel noted Pierre Fabre's submission that the letter was a safety letter to health professionals to highlight the under-dosing of Navelbine in advanced breast cancer. Pierre Fabre submitted that market research indicated that health professionals in the UK routinely under-dosed Navelbine patients and it had been asked by health professionals to send a reminder. In Pierre Fabre's view the provision of prescribing information might have implied that the communication was predominantly promotional in nature, whilst in its view the converse was true.

The Panel noted that the exemptions to the Code did not refer to 'safety letters'. The letter in question did not appear to meet any of the listed exemptions to the definition of promotion. Overall, the Panel considered that the letter in question was promotional. Its aim, according to Pierre Fabre, was to ensure the dosage regimen of single agent oral Navelbine was in accordance with its licence and that this was reflected in trust protocols. In the Panel's view the potential safety consequences of under-dosing were not such that they rendered the letter in question non promotional given the very broad definition of promotion in the Code. Doses lower than 80mg/m^2 weekly were recommended in certain circumstances. Prescribing information should have been included and a statement that adverse events should be reported. The Panel ruled breaches of the Code as these requirements had not been met.

The Panel considered that the size requirement in the Code for the non proprietary name was satisfied and no breach was ruled.

The Panel considered that the reference to 'advanced breast cancer' in the letter in question was not sufficiently qualified such that it was not a fair reflection of Navelbine's licensed indication for advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen and was inconsistent with the particulars listed in its SPC. A breach of the Code was ruled.

The Panel considered that the letter did not give sufficient weight to the importance of blood tests nor did it reflect the SPC requirement. Blood tests were not simply required when increasing the frequency of dosing as stated in the letter but on the day of each new administration. A breach of the Code was ruled. The Panel was very concerned about the failure to make the monitoring requirements clear and the potential impact on patient safety. It considered that this was a serious matter, particularly given Pierre Fabre's submission that the letter was a safety letter.
The Panel noted Pierre Fabre's submission that the use of 'may', within the claim, 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefits for patients' made it clear that not all patients might suffer from lack of efficacy due to under-dosing. It was, of course, perfectly reasonable for a company to promote its licensed dose. However, within the context of the letter the claim 'Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefit for patients' implied that there was data directly relevant to the use of Navelbine and the treatment of stage 3 and 4 advanced breast cancer relapsing or refractory to an anthracycline containing regimen and that was not so. Pierre Fabre provided data in patients with early stage breast cancer and non Hodgkin's Lymphoma. The word 'may' was insufficient to negate the primary impression. The claim was misleading and not capable of substantiation as alleged. Breaches of the Code were ruled.

With regard to calculations used in the bar chart headed 'Navelbine Oral dose and dose intensity' with the subheading 'Dose delivered per cycle (3 wks). Patient BSA 1.7m^2, capsules 80/30/20mg'. The Panel noted Pierre Fabre's submission that the complainant's example could not be delivered in practice and it did not take into account actual capsule strengths. Pierre Fabre had based the dose delivered on the amount of medicine that could practically be prescribed at each dose. The complainant and respondent agreed the example patient (1.7m^2) was appropriate. The Panel considered that the approach taken by Pierre Fabre was not unreasonable. Although a body surface area of 1.6m^2 gave a smaller dose delivered, on the narrow grounds alleged, the graph was not misleading. No breach of the Code was ruled.

The Panel noted its ruling that the letter was promotional and did not consider it was disguised in this regard. No breach of the Code was ruled.

A pharmacist complained about a letter sent by Pierre Fabre Limited regarding Navelbine (vinorelbine) oral dosing to oncology pharmacists practising within his service.

Navelbine was licensed as a single agent or in combination for the first line treatment of stage 3 or 4 non small cell lung cancer (NSCLC) and the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The letter dated 5 August was headed 'Under-dosing of Navelbine Oral' and stated that the only recommended dose of single agent Navelbine in advanced breast cancer was 80mg/m^2 weekly (following three doses at 60mg/m^2). The letter stated that efficacy was clearly associated with appropriate dosing and explained the consequences of under-dosing. It encouraged checks of local protocols to ensure that Navelbine oral was being used at the appropriate dose and included a bar chart.

COMPLAINT

The complainant explained that the letter was a direct mailing, which claimed to make 'factual, accurate, informative announcements and reference material concerning licensed medicines', however, it did not do so without making 'product claims'. The complainant stated that had the letter stated 'We would like to draw your attention to the dosing in the summary of product characteristics (SPC) and we have no evidence that other schedules are as effective' it would have achieved the same effect.

The complainant alleged a number of breaches of the Code.

1 Clause 4.1

The complainant stated that the letter could not be classed as an abbreviated advertisement because it was an A4 page with a surface area of 623sqcm exceeding the limit of 420sqcm. No prescribing information was provided other than the content of the letter provided.

The complainant noted that there was no information provided about:

- a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the SPC, together with a statement that prescribers should consult the SPC in relation to other adverse reactions
- the cost (excluding VAT) of either a specified package of the medicine to which the advertisement related, or a specified quantity or recommended daily dose, calculated by reference to any specified package of the product, except in the case of advertisements in journals printed in the UK which have more than 15 per cent of their circulation outside the UK and audiovisual

advertisements and prescribing information provided in association with them
- the legal classification of the product
- the number of the relevant marketing authorization and the name and address of the holder of the authorization or the name and address of the part of the business responsible for its sale or supply
- the date the prescribing information was drawn up or last revised.

In addition, the information provided in the letter for the following sections was weak:

- at least one authorized indication for use consistent with the summary of product characteristics
- a succinct statement of the information in the SPC relating to the dosage and method of use relevant to the indications quoted in the advertisement and, where not otherwise obvious, the route of administration.

The complainant pointed out that the indication in the letter was simply listed as 'Advanced Breast Cancer'; the marketing authorization was for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The complainant stated that the dosage information in the letter, which was the key point of the letter, referred to 80mg/m^2 weekly, following three doses of 60mg/m^2. There were a number of exclusions to dose escalation in the SPC related to full blood count, which were not listed in the letter. The letter stated that 'a blood test' was required for each dose when increasing frequency from doses 1 and 8 to doses 1, 8 and 15 but did not specify which tests were needed and did not highlight that that blood tests would define if dose escalation was appropriate.

The complainant referred to Clause 4.3 and stated that it was a relatively minor issue, however the approved name appeared directly below the most prominent display of the brand name, it did not appear with the same area as the brand name. The complainant referred to Clause 4.3 that 'All promotional material must include the prominent statement 'Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to [relevant pharmaceutical company]'.

No such statement appeared in the letter.

The complainant stated that while he/she did not believe the letter could be classified as abbreviated prescribing information, had it been it would have been required to contain the following statement: 'Information about this product, including adverse reactions, precautions, contra-indications and method of use can be found at [the address of the website referred to below] and state that prescribers are recommended to consult the summary of product characteristics before prescribing'. Given that the author was writing to highlight that prescribers were not following the SPC it might have been useful to direct prescribers to the SPC as well as medical information.

2 Clause 7

The complainant alleged that while Clause 7 did not specify that claims could not be made to the effect that a licensed dose was superior to an unlicensed dose of the same product without providing evidence, to make such a claim required evidence. The statement 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefit for patients' should have been accompanied by an evidence base, relevant to the use of anti-cancer agents in Stage 3 or 4 breast cancer, where the primary treatment objective was not always survival. The complainant was aware of very little evidence that substantiated that statement in this setting and none for vinorelbine dosing.

The complainant referred to Clause 7.8 and stated that the graph included in the letter used an example dose for a 1.7m^2 patient and whilst that was an appropriate example dose, the need to round to available capsule sizes meant that some adjustment of final dose given occurred. Had the graph compared 60mg/m^2 on days 1 and 8 it would have shown a 120mg/m^2 dose over the 21 day time frame in comparison to 80mg/m^2 on days 1, 8, 15 of 240mg/m^2. The difference would have been smaller both numerically and in proportion (120 to 240 was a 100% increase, 200 to 420 was a 110% increase). It was hard to be convinced that those values were not selected to make the difference as numerically large as possible. Had a 1.6m2 patient been selected for comparison, the comparison would have been 200mg vs 390mg.

3 Clause 12

The complainant referred to Clause 12.1 and alleged that the author had attempted to make the communication appear like a safety letter rather than promotional material. A clinician following the advice would use 50% more of the medicine and the complainant could not see how this had not resulted in promotion.

The complainant stated that his/her service used the SPC schedule but frequently did not dose escalate due to full blood count or due to other toxicity/ response profiles. The complainant was concerned that his/her clinicians would half read the letter and feel they should be dose escalating rather than optimising patient benefit with toxicity.

When writing to Pierre Fabre, the Authority asked it to respond in relation to Clauses 4.1, 4.3, 4.10, 7.8, and 12.1 of the Code as cited by the complainant. In addition, Pierre Fabre was also asked to consider Clauses 3.2, with regard to the indication stated in the letter in question, and Clauses 7.2 and 7.4 with regard to the evidence base to support the claim

'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefits for patients'.

RESPONSE

Pierre Fabre stated that it did not agree with the complainant's view that the letter in question was a promotional item. It was a safety letter sent via the medical department directly to health professionals in oncology to highlight the under-dosing of Navelbine in advanced breast cancer.

Pierre Fabre submitted that it had conducted market research, which showed that around 90% of patients were on an unlicensed low dose schedule, 60mg/m^2 on day 1 and day 8 every three weeks, vs a recommended dose of 80mg/m^2 every week (explained further below). The other 10% of patients were reported to receive a weekly dose of 60mg/m^2; which still fell short of the recommended 80mg/m^2 weekly schedule.

Pierre Fabre submitted that it had also been asked by health professionals to send a reminder on the appropriate dosing of Navelbine (details could be supplied if necessary), for patients with advanced breast cancer.

Pierre Fabre submitted that if it had included prescribing information along with the safety letter, it might have given the impression that the communication was predominately promotional in nature, while the converse was true. Moreover, Pierre Fabre did not want the nature of the safety letter to be classified as a promotional 'Dear Doctor' letter. The content was non-promotional, based on facts, which could be substantiated. Any product branding was also deliberately removed to ensure that the letter was seen as a non-promotional item. Given that the nature and the intent of the letter was non-promotional, Pierre Fabre contested the additional concerns of the complainant in relation to the provision of the information listed in Clause 4.2 ie in summary a legal classification, the number of the relevant marketing authorization and the name and address of the holder of the authorization, the date the prescribing information was drawn up or last revised, at least one authorized indication for use and succinct statement of the information in the summary of product characteristics (SPC) relating to the dosage and method of use.

Pierre Fabre believed that the safety letter was non-promotional and thus excluded it from the requirement to include prescribing information that would typically accompany a promotional item. Pierre Fabre denied a breach of Clause 4.1.

Similarly, Pierre Fabre submitted that Clauses 4.3 and 4.10 did not apply and it thus denied a breach of those clauses.

Pierre Fabre stated that although its products were provided with the SPC, the market research data indicated that under-dosing was prevalent. Pierre Fabre acknowledged that inclusion of the SPC would enable quicker referencing by the recipient, and so it would include SPCs in future safety communication.

With regard to Clause 3.2, Pierre Fabre reiterated that in its view the letter was not promotional. Moreover, it had not strayed outside Navelbine's marketing authorization. The safety letter focused on the under-dosing of Navelbine, within its licenced indication for advanced breast cancer. Thus, Pierre Fabre denied a breach of Clause 3.2.

Pierre Fabre stated that efficacy of cancer chemotherapy was generally established on the basis of randomised controlled clinical trials evaluating a particular medicine or combination using a specific dose and schedule. This was not only specific for advanced breast cancer, but could be clearly demonstrated in other forms of other malignancies.

Navelbine oral was authorised as a single agent for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen. The first three administrations were approximated to 60mg/m^2 once weekly, after which consequent doses were approximated to 80mg/m^2 once weekly. This titration should be routinely carried out, except in patients for whom the neutrophil count dropped below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first three administrations of 60mg/m^2. Pierre Fabre noted that it had clearly stated in the letter that blood tests should be carried out prior to escalation of dose, to ensure the wellbeing of patients.

The optimal dose of Navelbine oral was investigated in a dose-finding phase I study (Bonneterre *et al* 2001). The recommended dose of oral vinorelbine for further trials was defined at 80 mg/m^2/week. The study had three respective arms, 60mg/m^2, 80mg/m^2 and 100mg/m^2 dosing regimens. The results indicated that 80mg/m^2 was the most appropriate dose, with 4 tumour responses. 60mg/m^2 was considered ineffective in comparison to 80mg/m^2, as it did not yield any responses, while the 100mg/m^2 arm had 2 tumour responses. Therefore, the 80mg/m^2 weekly was the more efficacious dose (after the initial dose loading of 60mg/m^2) for patients with advanced breast cancer. This was the recommend dose for patients with stable neutrophil counts.

Pierre Fabre stated that there existed compelling preclinical and clinical evidence to indicate that reduction in standard dose intensity might compromise disease-free and overall survival in the curative setting in patients with cancer (Lyman *et al*, Budman *et al*, 1998, Lepage *et al* 1993). Pierre Fabre also referred to a figure and table in Gurney (2002).

Pierre Fabre submitted that the impact of inadvertent under-dosing on adjuvant chemotherapy for stage 2 breast cancer could be summarised by the following:

- Halving the dose of CAF (cyclophosphamide, doxorubicin, and fluorouracil) caused a reduction in the 5-year survival from 79 to 72% (absolute reduction=7%) (Budman *et al*).

Assuming that (conservatively) 30% of patients who

received CAF for stage 2 breast cancer were under dosed because of conventional dosing, absolute reduction in 5-year survival might be 30 of 7% = 2.1%, which was a 17.5% relative reduction in survival (Gurney).

Pierre Fabre stated that if it were to focus on the delivered dose intensity (total dose delivered over time to complete chemotherapy) and the relative dose intensity (ratio of delivered dose intensity to standard dose intensity and could be expressed as a percentage); there had been a clearly demonstrable relationship between survival and relative dose intensity (RDI) in a number of retrospective studies in patients with early stage breast cancer and Non-Hodgkin's Lymphoma (NHL). Details were provided.

Pierre Fabre submitted that the claim 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit the potential survival benefits for patients' had clearly been demonstrated by the evidence provided and was not misleading. Moreover, 'may' indicated that not all patients might suffer from lack of efficacy due to under-dosing. It was accurate, balanced, fair and capable of substantiation, thus Pierre Fabre denied a breach of Clauses 7.2 and 7.4.

With regard the graph included in the letter and the requirements of Clause 7.8, Pierre Fabre stated that it had used an average surface area of a patient as 1.7m^2 to calculate the doses in the safety letter as below:

Calculation used in safety letter (based on available capsule strength 20mg, 30mg & 80mg)

	60mg/m^2 d1, d8	**80mg/m^2 d1, d8**	**60mg/m^2 weekly**	**80mg/m^2 weekly**
Intended dose (1.7m2 x dose)	102mg d1,d8	136mg d1,d8	102mg d1,d8,d15	136mg/d1,d8,d15
Rounded dose (based on 20mg, 30mg and 80mg capsules	100mg d1,d8	140mg d1,d8	100mg d1,d8,d15	140mg d1,d8,d15
Rounded dose per cycle	200mg	280mg	300mg	420mg

d = day

This represented a 110% difference between the extremes of dose. While the complaint suggested that Pierre Fabre could have represented the doses in the following manner:

	60mg/m^2 d1, d8	**80mg/m^2 weekly**
Intended dose per cycle	120mg/m2	240mg/m2

This would represent a 100% difference between the extremes of dose. However, this calculation did not take into account the actual capsule strengths and could not be delivered in practice. If the cycle doses were converted to actual doses, then the same rounding up and down needed to be carried out in order to arrive at a delivered dose.

	60mg/m^2 d1, d8	**80mg/m^2 weekly**
Intended dose per cycle	120mg/m2	240mg/m2
Intended dose per cycle for patient (1.7m2)	204mg	408mg
Individual doses	102mg on d1 and d8	136mg on d1,d8,d15
Practically delivered doses	100mg (80mg and 20mg caps) on d1 and d8 = **200mg**	140mg (80mg and 2x30mg) on d1,d8 d15 = **420mg**

The dosing schedule, as demonstrated by the complainant, was focused on amount of medicine per cycle, while Pierre Fabre had chosen to base the dose delivered on the amount of medicine that could be practically prescribed at each dose.

Pierre Fabre submitted that it had kept within the spirit of the Code and had provided readers with a clear, fair, balanced view of the dose delivered per cycle. The company thus denied a breach Clause 7.8.

Pierre Fabre did not accept that the safety letter was disguised promotion; it was sent by the medical department to health professionals. The complaint conceded that it '… appear(s) as a safety letter than promotional material …'.

Pierre Fabre stated that the communication was a safety letter. As an ethical and patient focused company, it decided to send the safety letter after obtaining evidence that the majority of patients with advanced breast cancer that received oral

vinorelbine, were under-dosed. The company had not stated that all patients that were under-dosed 'would' and 'definitely' had their survival benefits curtained, it had merely stated that if patients were not receiving the most efficacious dose as per the SPC, they might limit their potential survival benefit. The letter did not make any exaggerated claims of improvement of survival benefit/outcomes – but instead focused on data that had been collected from Pierre Fabre's own studies and other health professionals (on different malignancies as well as breast cancer).

Pierre Fabre thus did not accept that it had disguised a safety letter as a promotional mailing, and denied a breach of Clause 12.1.

PANEL RULING

The Panel noted Pierre Fabre's submission that the letter in question was a safety letter meant for health professionals to highlight the under-dosing of Navelbine in advanced breast cancer. The letter was signed by the medical manager and sent to health professionals that worked in oncology. Pierre Fabre submitted that its market research had indicated that health professionals in the UK routinely under-dosed Navelbine patients and it had also been asked by health professionals to send a reminder on the appropriate dosing of Navelbine for patients with advanced breast cancer. In Pierre Fabre's view the provision of prescribing information might have implied that the communication was predominantly promotional in nature, whilst in its view the converse was true.

The Panel noted that the exemptions to the Code did not refer to 'safety letters'. The letter in question did not appear to meet any of the listed exemptions to the definition of promotion. The Panel further noted that the letter in question had not been sent at the request of the MHRA nor had it been triggered as a result of a safety report to the company or analysis of patient safety data. The Panel was concerned that the very limited market research supplied did not appear to support the company's position about suboptimal dosing. In addition, no supporting material had been supplied in relation to the statement in the letter that many trust protocols specified a regimen that Pierre Fabre only recommended when Navelbine was used in combination with other anti-cancer agents rather than that licensed for single agent use. Whilst noting its concerns about the market research, the Panel nonetheless considered that suboptimal dosing was an important issue but any communication in this regard had to comply with the Code. The Panel noted that discussing safety matters or adverse events did not *ipso facto* mean that a communication was non promotional. Each case had to be decided on its individual circumstances. The Panel noted the broad definition of promotion in Clause 1.2 ie any activity which promoted the administration, consumption, prescription, purchase, recommendation, sale, supply or use of a company's medicine. Overall, the Panel considered that the letter in question was promotional. Its aim, according to Pierre Fabre, was to ensure the dosage regimen of single agent oral Navelbine was in accordance with its licence and that this was reflected in trust protocols. The letter in question referred to the brand name seven times. In the Panel's view the potential safety consequences of under-dosing were not such that they rendered the letter in question non promotional given the very broad definition of promotion in Clause 1.2 of the Code. Doses lower than 80mg/m^2 weekly were recommended in certain circumstances. The Panel considered that the promotional nature of the letter triggered the requirement to provide prescribing information, as listed in Clause 4.2; the letter should also have included a statement that adverse events should be reported. The Panel noted that these requirements had not been met and ruled breaches of Clauses 4.1 and 4.10.

With regard to the allegation that while the approved name appeared directly below the most prominent display of the brand name, it did not appear with the same area as the brand name the Panel noted the most prominent display of the brand name was within the heading 'Under-dosing of Navelbine Oral' with the non-proprietary name in smaller font size appearing on the line below 'Navelbine® Oral (vinorelbine soft capsules)'. Both the brand name and non proprietary name were in bold type. The Panel noted the requirements of Clause 4.3 that the size of the non proprietary name or the list of active ingredients should occupy a total area no less than that taken up by the brand name or in type of a size such that the lower case 'x' was no less than 2mm in height. The Panel noted that whilst the total size occupied by the non proprietary name appeared to be less than that of the brand name the font size was such that lower case letters were not less than 2mm in height. The Panel considered that the size requirement for the non proprietary name was thus satisfied and no breach of Clause 4.3 was ruled.

The Panel noted that beneath the heading 'Under-dosing of Navelbine Oral' the first paragraph stated 'The only recommended dose of single agent Navelbine Oral in advanced breast cancer is 80mg/m^2 weekly (following three doses at 60mg/m^2)'. Navelbine Oral was indicated as a single agent or in combination for, *inter alia*, the treatment of advanced breast cancer, stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen. The Panel considered that the reference to 'advanced breast cancer' in the letter in question was not sufficiently qualified such that it was not a fair reflection of Navelbine's licensed indication for advanced breast cancer and was inconsistent with the particulars listed in its SPC. A breach of Clause 3.2 was ruled.

With regard to the final paragraph of the letter which began 'When increasing the frequency of dosing please be aware that a blood test is recommended before each dose', the Panel noted Section 4.4 of the Navelbine SPC, Special warnings, stated, *inter alia*, 'Close haematological monitoring must be undertaken during treatment (determination of haemoglobin level and the leucocyte, neutrophil and platelet counts on the day of each new administration). Dosing should be determined by

haematological status ...'. In addition, Section 4.2 of the Navelbine SPC, Posology and method of administration, stated, *inter alia*, that 'Beyond the third administration, it is recommended to increase the dose of Navelbine to 80mg/m^2 once weekly except in those patients for whom the neutrophil count dropped once below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first three administrations at 60mg/m^2'. The Panel considered that the letter was misleading as alleged. It did not give sufficient weight to the importance of blood tests nor did it reflect the SPC requirement. Blood tests were not simply required when increasing the frequency of dosing as stated in the letter but on the day of each new administration. A breach of Clause 7.2 was ruled. The Panel was very concerned about the failure to make the monitoring requirements clear and the potential impact on patient safety. It considered that this was a serious matter, particularly given Pierre Fabre's submission that the letter was a safety letter.

The Panel noted Pierre Fabre's submission that the use of 'may', within the claim, 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefits for patients' made it clear that not all patients might suffer from lack of efficacy due to under-dosing. The Panel noted that the data submitted by Pierre Fabre indicated that in certain patient populations the dose of cytotoxic treatments was important in relation to disease free survival and overall survival. Bonneterre *et al*, a phase 1 and pharmacokinetic study of oral vinorelbine in first and second line patients with locally advanced or metastatic breast cancer found that no response was observed, in the six evaluable patients treated, with 60mg/m^2/week. The SPC referred to 60mg/m^2 dose, whether that be as an initial dose for three administrations or following certain neutrophil counts or patients with liver insufficiency. It was, of course, perfectly reasonable for a company to promote its licensed dose. However, nonetheless, the Panel considered that within the context of a letter which discussed the recommended dose of single agent Navelbine oral in advanced breast cancer the claim 'Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefit for patients' implied that there was data directly relevant to the use of Navelbine and the treatment of stage 3 and 4 advanced breast cancer relapsing or refractory to an anthracycline containing regimen and that was not so. Pierre Fabre provided data in patients with early stage breast cancer and non Hodgkin's Lymphoma. The Panel also considered that the word 'may' was insufficient to negate the primary impression. The claim was misleading and not capable of substantiation as alleged. A breach of Clauses 7.2 and 7.4 was ruled.

With regard to calculations used in the bar chart headed 'Navelbine Oral dose and dose intensity' with the subheading 'Dose delivered per cycle (3 wks). Patient BSA 1.7m^2, capsules 80/30/20mg'. The bar chart showed four bars. The first two were data for 60mg/m^2 and 80mg/m^2 administered on d1 d8 and q21 and the third and fourth bar showed data for 60mg/m^2 weekly and 80mg/m^2 administered weekly. The 80mg/m^2 weekly bar was labelled 'Recommended dose'. An asterix to each 80mg/m^2 dose read 'First cycle/3weeks at 60mg/m^2'. In relation to this graph, the complainant alleged that use of a 1.7m^2 patient required a greater dose per cycle than if a 1.6m^2 patient had been used. The Panel noted Pierre Fabre's submission that the example chosen by the complainant could not be delivered in practice and it did not take into account actual capsule strengths. Pierre Fabre had based the dose delivered on the amount of medicine that could practically be prescribed at each dose. The complainant and respondent agreed the example patient (1.7m^2) was appropriate. The Panel considered that the approach taken by Pierre Fabre was not unreasonable, the example dose for a patient with a body surface area of 1.7m^2 was appropriate. Although a body surface area of 1.6m^2 gave a smaller dose delivered, on the narrow grounds alleged, the graph was not misleading. No breach of Clause 7.8 was ruled.

The Panel noted it's ruling that the letter was promotional and did not consider it was disguised in this regard. No breach of Clause 12.1 was ruled.

During its consideration of this case the Panel was concerned about a number of matters as follows.

Firstly, the Panel was concerned that the market research data provided did not indicate that health professionals in the UK routinely under-dosed their patients with single agent Navelbine oral, in advanced breast cancer, which was Pierre Fabre's rationale for the letter in question. The Panel did not have a complete copy of the market research and it was unclear which country the data applied to. The data did not segment patients receiving the first three administrations of Navelbine oral, those receiving subsequent administrations and those in whom the dose could not be escalated due to a reduced neutrophil count. In the Panel's view the average dose administered in accordance with the licensed indication could not be established from the market research data provided. In addition, the data did not appear to support the submission that patients were being under-dosed. The Panel queried whether the claim for under-dosing was capable of substantiation.

Secondly, the Panel was concerned about the graph as the doses of 60mg/m^2 and 80mg/m^2 at d1, d8, and q21 appeared to be inconsistent with the single agent licensed regimen of the first three administrations at 60mg/m^2 once weekly and the recommended increase in dose to 80mg/m^2 in certain patients. The Panel noted its comments above regarding the material to support Pierre Fabre's position regarding sub optimal dosing and that the requirement for monitoring prior to each new administration was not sufficiently clear, the Panel considered that it was not clear from the graph that the appropriate dose would depend on patient

experience, tolerability and stage of treatment. The Panel also noted that the inclusion of 'recommended dose', under 80mg/m^2 weekly drew attention to that dose regimen; which would not be appropriate for all patients.

The Panel requested Pierre Fabre be advised of its concerns on the two points outlined above.

Complaint received **16 August 2014**

Case completed **30 October 2014**

Case AUTH/2732/9/14

VOLUNTARY ADMISSION BY JANSSEN

Invokana letter misleading for some GPs

Janssen voluntarily admitted that it had sent some GPs a misleading 'Dear Doctor' letter about its antidiabetic medicine, Invokana (canagliflozin).

In accordance with Paragraph 5.6 of the Constitution and Procedure the matter was treated as a complaint.

Janssen explained that the letter was sent to GPs in 150 clinical commissioning groups (CCGs). The letter stated that Invokana had been approved by the local formulary process and was available to be prescribed in accordance with guidance from the National Institute for Health and Care Excellence (NICE), however in 39 CCGs only consultant physicians could initiate Invokana therapy. Janssen submitted that for these CCGs it had thus not accurately portrayed the local situation and believed that it might have breached of the Code.

Janssen stated that following a complaint from a GP it realised the error and immediately put in place a corrective action plan to apologise for and correct the inaccuracy. Janssen stated that it took its responsiblities under the Code very seriously and regretted this unfortunate error and would implement steps to ensure it did not recur.

Further details from Janssen are given below.

The Panel noted that the letter, sent to the GPs, was headed 'Invokana (canagliflozin) available to prescribe in [named CCG]'. The letter began 'I am writing to inform you that following the NICE Technology Appraisal Guidance (TAG) for the use of Invokana (canagliflozin) in England and Wales, it has been approved by your local formulary process and is available to prescribe in [named CCG].' The Panel noted that for some recipients this was not so; the letter had been sent to some GPs where, although Invokana was on the CCG formulary, it was not available for them to prescribe. The Panel considered that the letter was misleading in this regard. A breach of the Code was ruled. The Panel further considered that the error was likely to have created confusion and additional work in some CCGs. The Panel considered that high standards had not been maintained and a breach of the Code was ruled.

Janssen voluntarily admitted that it had sent some GPs a misleading 'Dear Doctor' letter (ref PHGB/VOK/0714/0029a) about its antidiabetic medicine, Invokana (canagliflozin).

In accordance with Paragraph 5.6 of the Constitution and Procedure the matter was treated as a complaint.

VOLUNTARY ADMISSION

Janssen explained that the letter was emailed or sent by post on 16 September to GPs in 39 clinical commissioning groups (CCGs) in England. The letter stated that Invokana had been approved by the local formulary process and was available to be prescribed in accordance with guidance from the National Institute for Health and Care Excellence (NICE), however GPs in those particular CCGs did not necessarily have freedom to prescribe Invokana. Janssen submitted that it had thus not been accurate in its portrayal of the local situation and believed that it might have breached Clause 7.2.

The same letter was also posted or emailed on the same day to GPs in 111 CCGs where this prescribing freedom existed and in that regard Janssen believed these letters were accurate.

Janssen considered that as the breach was caused by human error, and not picked up by an existing company procedure, it had not maintained its usual high standards in relation to compliance with the Code and therefore it also believed that it might have breached Clause 9.1.

Copies of the letter and the email, as well as their certificates, were provided.

Janssen stated that following a complaint from a GP prescribing lead of a CCG it realised the error and immediately put in place a plan to contact all involved CCGs to apologise and offer remedial actions, including the sending of a further email or letter, after agreement of the relevant CCG, to correct the inaccuracy.

Janssen stated that it took its responsiblities under the Code very seriously and sincerely regretted this unfortunate error and would implement steps to ensure it did not recur.

Janssen was asked to comment on this matter in relation to Clauses 7.2 and 9.1 of the Code.

RESPONSE

Janssen explained that the letter was intended to let GPs know that Invokana was on formulary and available to prescribe in their CCGs. This information was what the CCG made availalbe to all prescribers within the CCG, as part of its requirement to implement NICE-approved medicines. NICE guidance for Invokana was published on the 25 June 2014.

CCGs indicated formulary approval via a tiered, generally colour coded system, whereby at one end of the spectrum a GP had full freedom

to initiate and prescribe and on the other end, although Invokana was available on formulary, only consultant physicians could initiate a prescription. Through interactions with local stakeholders, the Janssen health economy liaison managers (HELMs) ascertained when Invokana had been approved by the CCG on local formulary and confirmed this via the CCG website where applicable (ie if formulary was published or immediately updated). If the CCG had not yet posted its formulary status online, Janssen got confirmation from when specialists and/or GPs could prescribe and sought guidance on when it could communicate this to GPs via the Janssen account managers (AMs). After every formulary approval, the Janssen local account team, led by the HELM, completed a tracker to confirm the local formulary status, this was then checked by the regional business managers and regional market access managers. The tracker was stored and updated on an internal Janssen site.

An unfortunate internal oversight meant that the letter at issue, which was intended to be sent to CCGs that had full GP freedom to prescribe, was sent to all CCGs where Invokana was on the formulary (ie it was sent in 39 CCGs where there was not full GP freedom to prescribe).

Janssen stated that it briefed its HELMs and AMs by telephone on 17 September to tell them about the issue and agree actions for the HELMs in terms of making the CCG prescribing leads aware of the error. This verbal briefing was followed by a written interal briefing to the HELMs on 18 September and to the AMs on the 24 September.

As of 6 October, senior Janssen staff had contacted four CCGs that had complained directly to the company, to apologise and discuss potential remedial actions.

Janssen submitted that all of the 39 CCGs that did not necessarily have GP freedom to prescribe Invokana had received an apology from the HELM for their respective regions and Janssen had offered to send a retraction letter and email to all GPs in the 39 CCGs and if accepted, it would agree the content with the individual CCG before it was sent. If a CCG prescribing lead requested any specific amends to the standard letter or email, it would be amended and certified by Janssen before being sent.

PANEL RULING

The Panel noted that the letter, sent to the GPs, was headed 'Invokana (canagliflozin) available to prescribe in [named CCG]'. The letter began 'I am writing to inform you that following the NICE Technology Appraisal Guidance (TAG) for the use of Invokana (canagliflozin) in England and Wales, it has been approved by your local formulary process and is available to prescribe in [named CCG].' The Panel noted that for some recipients this was not so; the letter had been sent to some GPs where, although Invokana was on the CCG formulary, it was not available for them to prescribe. The Panel considered that the letter was misleading in this regard. A breach of Clause 7.2 was ruled. The Panel further considered that the error was likely to have created confusion and additional work in some CCGs. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaint received **18 September 2014**

Case Completed **20 October 2014**

CODE OF PRACTICE REVIEW – November 2014

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

AUTH/2684/12/13	**Health professional v Galderma**	**Unsolicited emails**	**Two breaches Clause 9.1** **Two breaches Clause 9.9** **Audit required by the Appeal Board** **Public reprimand required by the Appeal Board** **Removed from the list of non member companies which have agreed to comply with the Code**	**Appeal by the respondent** **Report from the Panel to the Appeal Board** **Report from the Authority to the Appeal Board**	**Page 3**
AUTH/2685/12/13	**Anonymous, non contactable nurse v Galderma**	**Meeting arrangements**	**Breaches Clauses 2, 9.1 and 18.1** **Audit required by the Appeal Board** **Public reprimand required by the Appeal Board** **Removed from the list of non member companies which have agreed to comply with the Code**	**Appeal by the respondent** **Report from the Panel to the Appeal Board** **Report from the Authority to the Appeal Board**	**Page 11**
AUTH/2694/1/14	**Anonymous v Pharmacosmos**	**Promotion of Monofer**	**Breaches Clauses 7.11, 9.1, 23.1 and 23.2** **Removed from the list of non member companies which have agreed to comply with the Code**	**No appeal** **Report from the Authority to the Appeal Board**	**Page 18**
AUTH/2705/3/14	**Roche v Merck Serono**	**Presentation of Erbitux clinical trial results in a press release**	**Breach Clause 2** **Five breaches Clause 7.2** **Two breaches Clause 7.3** **Two breaches Clause 7.10** **Breach Clause 9.1** **Breach Clause 10.2** **Two breaches Clause 22.2**	**Appeal by respondent**	**Page 24**
AUTH/2714/5/14	**Consultant rheumatologist v Pfizer**	**Conduct of a representative**	**Breaches Clauses 9.1 and 15.2**	**Appeal by the complainant**	**Page 47**
AUTH/2715/5/14	Anonymous pharmacist v Lilly	Nurse education service	No breach	No appeal	Page 58
AUTH/2719/6/14	**Voluntary admission by Amgen**	**Nominated signatories**	**Breaches Clauses 14.1 and 14.4**	**No appeal**	**Page 66**
AUTH/2720/6/14	Anonymous v Genzyme	Conduct of a representative	No breach	No appeal	Page 68
AUTH/2722/7/14	**Anonymous Ex-employee v Orion Pharma**	**Respiratory review**	**Breaches Clauses 9.1, 18.1 and 18.4**	**No appeal**	**Page 72**

AUTH/2723/7/14	**Clinician v Napp**	**Promotion of BuTrans**	**Two breaches Clause 7.2** **Two breaches Clause 7.4**	**Appeal by both the complainant and the respondent** **Report from the Panel to the Appeal Board** **Suspension of items at issue pending the final outcome of the case required by Panel**	**Page 80**
AUTH/2724/7/14	**Tillotts v Ferring**	**Pentasa cost comparison chart**	**Breach Clause 7.2**	**No appeal**	**Page 100**
AUTH/2725/7/14	Member of the public v Roche	Newspaper article about Avastin	No breach	No appeal	Page 103
AUTH/2727/8/14	**Pharmacist v Pierre Fabre**	**Promotion of Navelbine**	**Breaches Clauses 3.2, 4.1, 4.10, 7.2 and 7.4**	**No appeal**	**Page 106**
AUTH/2732/7/14	**Voluntary admission by Janssen**	**Invokana letter misleading for some GPs**	**Breach Clauses 7.2 and 9.1**	**No appeal**	**Page 114**

PMCPA | Prescription Medicines Code of Practice Authority

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.