NUMBER 78 November 2012

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.

ETHICAL STANDARDS IN HEALTH AND LIFE SCIENCES GROUP

The Ethical Standards in Health and Life Sciences Group (ESHLSG) is a multi stakeholder group of healthcare organisations. The quarterly meetings are co chaired by the Presidents of the Royal College of Physicians and the ABPI. The group includes representation from the medical, pharmacy and nursing communities, the NHS Confederation as well as medical device and diagnostic industries in the UK. It was established following work and discussions arising out of the publication of the Royal College of Physicians' working party 2009 report, Innovating for Health – Patients, physicians, the pharmaceutical industry and the NHS. The ABPI is a member. The General Medical Council and the PMCPA have observer status. The role of the group is to evolve the relationship between health professionals and commercial life science organisations to ensure that it meets the expectations of stakeholders and creates a platform for increased collaboration and partnership for the benefit of patients.

The group is currently running a survey to look at health professionals' attitudes to industry supported medical education. The group will shortly issue a consultation on the disclosure of payments to health professionals. Further details on the role of the group and its activities can be found on its website (eshlsg.org).

THE APPEAL PROCESS

Before submitting an appeal, the parties should read the Guidelines on Appeal Procedures, provided by the Authority with the notification of the Panel's rulings. That guidance is also available on the Authority's website (www.pmcpa.org.uk) together with other relevant advice. Well grounded and well prepared appeals have a greater chance of being successful and both parties should ensure that all points are covered in their written submissions. No new material can be added at the appeal hearing itself.

Appellants should, wherever possible, attend the hearing of their appeal; the person most closely involved with the issue should make attendance a priority. Paragraph 4.7 of the Constitution and Procedure states that the Chairman of the Code of Practice Appeal Board can invite certain persons to attend an appeal. Both parties are entitled to attend an appeal and make a short presentation to state their position.

The presentations, which must be submitted to the Authority three working days before the hearing, will be swapped between the parties. If a presentation contains data not previously submitted in writing, the relevant party will be contacted and asked whereabouts in the written submissions the data appears. If the data has not previously been submitted, the party concerned will be asked to remove it. The Chairman has the last word on such matters.

At the hearing itself, once the parties have each made their presentations and answered questions from the Appeal Board, the appellant will be asked to make a closing remark and in that regard it is helpful to have prepared a short summary statement.

If either party has any questions about a forthcoming appeal, they should not hesitate to contact the Authority for informal advice.

TWO HAPPY EVENTS

Vicky Edgecombe, Communications Manager, has a son, David, who was born in October. Vicky will be on maternity leave until next year. Peter Clift, Executive Officer, has a second daughter, Erin, who was born in August. The Authority sends its best wishes to both families.

GOODBYE AND GOOD LUCK

Ros Henley, who has been with the Authority since June 2011 as Deputy Secretary, will be leaving early next year to start a new job with a pharmaceutical company. The Authority thanks Ros for all her hard work and wishes her every success in her new role. The Authority is looking for a replacement and further details are available on the website.

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 seminars comprise a full day course offering 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:

Tuesday, 29 January

Short training sessions on the Code or full all 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 email 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 email 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
Ros Henley: 020 7747 8883

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

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

CASE AUTH/2474/1/12

GLAXOSMITHKLINE EMPLOYEE v GLAXOSMITHKLINE

Promotional activities and training

An employee of GlaxoSmithKline UK complained about the company's promotion of, and/or staff training on, Revolade (eltrombopag), Seretide (fluticasone/salmeterol) and ReQuip XL (ropinirole).

The complainant alleged that a GlaxoSmithKline representative had promoted the unlicensed use of Revolade for myeloid fibrosis via an individual funding request (IFR). Revolade was indicated for immune (idiopathic) thrombocytopenic purpura (ITP).

The detailed responses from GlaxoSmithKline are given below.

The Panel noted that the subject matter of the representative's email, which was sent to a consultant at the request of the consultant's secretary, read 'Request for an appointment re an IFr submission for a patient with Myeloid Firosis [*sic*]'. The email referred to a telephone conversation with the consultant's secretary and suggested dates for an appointment to 'discuss putting together the IFR for your patient with Myeloid Fibrosis'.

The Panel noted the licensed indication for Revolade. The Panel also noted that according to GlaxoSmithKline, the consultant had asked the representative for information about Revolade to support a funding request for a patient with chronic ITP as the patient had myelofibrosis and asked for information about myelodysplastic syndrome and bone marrow failure syndromes. The representative sent the latter request to GlaxoSmithKline's medical information function for a response.

The Panel noted that whilst the subsequent meeting discussed an IFR for the use of Revolade in chronic ITP, the subject matter of the email in question referred to myeloid fibrosis as the representative had considered that this was the only way to identify the reason for the meeting. The Panel queried whether this was so. In his/her signed statement the representative acknowledged that the email could have been misconstrued and that during the subsequent meeting the consultant had the patient in mind but the representative had stressed that they could only talk about the use of Revolade in chronic ITP.

Whilst the email did not expressly refer to Revolade, it was an integral part of a series of communications about the medicine. The IFR referred to in the subject matter of the email was in relation to Revolade. The Panel considered that whilst there was no evidence that the subsequent meeting was unacceptable in relation to the requirements of the Code, the subject matter of the email in question implied that the IFR related to Revolade and its use in myeloid fibrosis and consequently promoted Revolade outside its licensed indication as alleged. A breach of the Code was ruled.

The Panel considered that the representative should have been mindful of the impression given by the subject matter of the email and noted the representative's acknowledgement that it could have been misconstrued. High standards had not been maintained in this regard by the representative and a breach of the Code was ruled. There was, however, no evidence that the company had failed to maintain high standards and the Panel ruled no breach of the Code including no breach of Clause 2.

The complainant alleged that a tactical brand plan for Revolade led representatives to promote the product for unlicensed indications.

The Panel noted that the Revolade brand plan and its covering email were provided to two GlaxoSmithKline employees in response to a request for background brand strategy information from a GlaxoSmithKline trainer to satisfy the training needs of a hospital healthcare business manager (HHBM). The author of the email in question was an individual aligned to the brand planning team.

The covering email explained that the global tactical brand plan was for background use only and that a UK brand plan would be produced subsequently. The email outlined six outputs from a UK brand plan day including 'Clinical Experience and KEG [Key Evidence Generation] Explore data to cover use in presurgery - off license but reported to team'. The Panel noted that it had to consider whether the provision of the global tactical brand plan and covering email to the HHBM (who was not a member of the brand planning team) encouraged the promotion of Revolade beyond its licence.

According to GlaxoSmithKline HHBMs worked with senior non-clinical NHS staff on local access to medicines and budget management; they were only expected to have a basic knowledge of GlaxoSmithKline medicines. They could offer support to specific brands by having discussions with payer customers. The role of the HHBMs was further described as, *inter alia*, driving the 'growth of GlaxoSmithKline brands through excellent account management in secondary care', and at the launch of the product they would 'lead and support the account team to drive rapid uptake of the brand, including plans for formulary inclusion'. Reference was made to subsequent commercialisation. Key contacts for most HHBMs included senior pharmacists.

The Panel noted that the first slide of the Revolade global tactical brand plan made it clear that all materials were subject to local review and approval. The plan discussed the disease, global market access challenges, growth strategies and performance measurement etc. There was no reference to off-licence use. The Panel did not consider that the

provision of the global tactical brand plan to the HHBM was contrary to the Code as alleged; it did not discuss unlicensed use of Revolade and the covering email made it clear that it was provided for background reading only. The Panel did not consider that there had been a failure to maintain high standards in relation to the content of the global tactical brand and its provision to an HHBM; no breach of the Code was ruled.

The Panel noted that the subject of the covering email was 'Brand Plan Global: Revolade reading only: [name]'. A bullet point read 'Explore data to cover use in presurgery – off licence but reported to the team'. GlaxoSmithKline explained that as this off-licence use had been reported to the brand team, its medical department would explore data generation and medical information responses. The Panel considered that the email did not make this clear and without the benefit of GlaxoSmithKline's explanation the bullet point in question was open to misinterpretation by field based staff who did not participate in the meeting. The Panel therefore did not accept GlaxoSmithKline's submission that as it was a medical department issue, no further qualification was needed and no follow up with the email recipients would have been necessary. The outputs of the meeting had been disseminated beyond the UK Brand Plan team to, *inter alia*, a member of a field based team without the benefit of GlaxoSmithKline's detailed explanation. The covering email, including the subject title, made it clear that the global brand plan was for background only but no such qualification was applied to the outputs of the UK brand planning meeting.

The Panel was concerned about the unqualified reproduction of the outputs from the UK brand meeting in the covering email which referred to the unlicensed use of Revolade and its provision to an HHBM who was not a member of the UK brand planning team. The Panel considered that the dissemination of such material to an HHBM who, *inter alia*, would have product related discussions with payer customers, would have to comply with the Code. The trainer to whom the email was also sent could not recall discussions following the email but had confirmed that approved materials were used for all subsequent training for the HHBM. The Panel considered that the unqualified reference to unlicensed use in the email in question together with its provision to an HHBM who was not a member of the UK brand planning team meant that high standards had not been maintained; a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a sign of particular censure; no breach of Clause 2 was thus ruled.

The complainant alleged that the hospital business manager's team falsified a Seretide product certification examination. All of the managers sat the product knowledge test at the same time and the answers were read out by a team member as instructed by a manager. This deliberate action, following limited training, meant that the hospital business managers were not adequately trained on Seretide when they engaged with customers. The complainant subsequently provided additional material in support of this allegation.

The Panel noted that it firstly had to consider whether the HHBMs satisfied the definition of a representative under the Code. The Code defined a representative as anyone calling on members of the health professions and administrative staff in relation to the promotion of medicines. This was a wide definition and could cover the activities of those employees that companies might not call or consider as representatives.

The Code defined promotion as 'any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines'.

The Panel noted GlaxoSmithKline's submission that the HHBMs worked with senior non-clinical NHS staff on, *inter alia*, formularies. They could also offer additional support to specific brands by having discussions with senior managers and payers for which they underwent product training as there was a possibility that HHBMs would be required to have discussions with senior managers and payers, and the training event in question was designed to satisfy this additional training need in relation to Seretide. The Panel noted that the personal development plans (PDPs) provided referred primarily to a facilitation and account mapping role in relation to Seretide.

The Panel noted GlaxoSmithKline's submission that HHBMs could offer additional support to specific brands by having discussions with payer customers. In this regard the Panel also noted that a document provided by the complainant entitled 'The role of the HHBM within the Respiratory Market Access' stated that within specific accounts identified by the area business manager (ABM) the HHBM would proactively raise Seretide to discuss the current situation. The Panel noted the HHBMs' broad role as set out in the papers provided by both parties. The Panel noted the definitions of promotion and representative in the Code as set out above and considered that merely because HHBMs did not interact with prescribers did not mean that such interactions were not promotional as defined in the Code. The Panel considered that a limited aspect of the HHBMs' role was likely to involve discussion of specific medicines, and taking all the circumstances into account, the Panel considered that, in relation to this part of their role, they acted as representatives as set out in the Code.

The Panel noted that the parties' accounts of the training event differed. It was difficult to determine precisely what had occurred. The Panel noted that the complainant bore the burden of proving his/her complaint on the balance of probabilities. The complainant alleged that it was not a *bona fide* training event and the answers were read out to participants. GlaxoSmithKline explained that it was a knowledge consolidation event rather than evaluation, at the end of an online product training course. The Panel noted that, according to the unsigned witness statements provided by GlaxoSmithKline, whilst at least one participant completed the test alone, the majority appeared to have completed the informal test collaboratively, with the benefit of discussion.

The Panel noted that the Code required representatives to be given adequate training and have sufficient knowledge to enable them to provide full and accurate information about the medicines which they promoted. The Panel considered that it was acceptable to run informal training sessions to consolidate rather than evaluate participants' product knowledge as described by GlaxoSmithKline. However, the overall training package must satisfy the relevant requirements of the Code. The complaint on this point related solely to the specific training event. The Panel noted GlaxoSmithKline's submission that further extensive training was provided to HHBMs. The Panel did not consider that the conduct of the training event in question was such that the company had failed to satisfy the broader product training requirements of the Code as alleged. No breach of the Code was ruled. The company had not failed to maintain high standards in relation to the event; no breach of the Code was ruled. The Panel consequently ruled no breach of Clause 2.

The complainant alleged that at another training event GlaxoSmithKline employees falsified another examination to ensure compliance with the Code. The team had received repeated text messages in the preceding weeks which set out the questions and answers within the examination. The team sat the examination at the same time and the answers were read out by a manager. The complainant submitted that many of the questions in the test, particularly around the NHS, were very difficult and that he/she had never received any formal relevant training.

The complainant alleged that the HHBMs were not trained to a standard that allowed them to have accurate discussions with customers.

The Panel noted that the complaint concerned the conduct of the pilot annual product knowledge review. The Panel noted its comments above about the role and status of HHBMs and considered that they applied here.

The Panel noted that, once again, the parties' accounts differed and it was difficult in such circumstances to determine precisely what had occurred. The Panel noted that the complainant bore the burden of proving his/her complaint on the balance of probabilities.

The Panel noted GlaxoSmithKline's submission that the annual product knowledge review was first piloted with the HHBMs in 2011. The process had been carried out successfully over a number of years with representatives to test their level of product knowledge.

The Panel noted that GlaxoSmithKline had provided a number of unsigned witness statements from HHBMs who took part in the pilot test. All interviewees refuted the allegation that answers were read out as alleged. The witness statement of the HHBM national business manager explained that on the day of the test he decided to run it as an open book test with access to online information for participants. Some participants were helped where to look online. The test was described as a knowledge and information seeking test to see how they got on. It was acknowledged that this activity needed to be run differently next time.

The Panel considered that in principle it was acceptable to run pilot training sessions to inform and improve the overall product training package. However, the overall training package should comply with the Code. The complaint on this point related solely to the training event at issue. The Panel noted GlaxoSmithKline's submission that further extensive training was provided to HHBMs. The Panel did not consider that the conduct of the second training event demonstrated that the company had failed to satisfy the broader product training requirements of the Code; no breach of the Code was ruled. The Panel consequently ruled no breaches of the Code including no breach of Clause 2.

The complainant alleged that GlaxoSmithKline's overall product training standards were below that expected by the Code. The complainant subsequently submitted further material which mainly concerned the promotion of GlaxoSmithKline's medicines to NHS customers by representatives who had not received formal and certified internal training. The complainant also provided documents about the promotion of ReQuip XL using integrated healthcare managers (IHMs), although those IHMs had never received any formal training. The complainant provided a copy of a presentation which he/she found wholly unethical as it was entitled 'Revolade Smashing targets'. The complainant referred to an email from the Revolade marketing team to the representatives that revealed the locations and names of doctors using Revolade under the named patient programme.

The complainant also alleged that the lack of adequate training was evidenced in personal development plans.

The Panel noted GlaxoSmithKline's submission that its representatives were thoroughly and comprehensively trained on Seretide. Training slides and other relevant material were provided. The complainant had provided no material in support of his/her allegation on this point. The Panel considered that on the material before it there was no evidence to demonstrate that GlaxoSmithKline's sales representatives were not given adequate training and sufficient scientific knowledge to enable them to provide full and accurate information about the medicines they promoted. No breach of the Code was ruled.

In relation to HHBMs and Seretide, the Panel noted its comments about the role of the HHBMs and the role of the HHBMs with regard to Seretide as described in the document 'The role of the HHBM within Respiratory Market Access' which referred to specific circumstances where HHBMs were contracted to proactively discuss Seretide. The Panel noted that neither the document nor its covering email limited such discussion to financial implications as stated by GlaxoSmithKline. The document stated that the knowledge level required for HHBMs generally included 'a basic understanding

of Seretide to include the SPC [summary of product characteristics], preparations and prices'. The undated document was circulated to HHBMs in April 2011 and the covering email referred to its previous circulation to HHBMs in February 2011.

The Panel noted GlaxoSmithKline's submission that when HHBMs had discussions with payer customers to support specific brands, they underwent product training. The Panel noted GlaxoSmithKline's submission that in 2011 HHBMs received 20 days of training of which 13 were product training which GlaxoSmithKline considered provided them with knowledge above and beyond that required by their role. The Panel noted that the HHBM training for Seretide in 2011 comprised product training on two separate days (neither were full days). In addition, the HHBM team did distance learning for Seretide and brand managers delivered updates at HHBM team meetings. The Panel noted GlaxoSmithKline's submission about the need for further training to enable HHBMs to have more detailed discussions. The Panel noted that GlaxoSmithKline had, in effect, acknowledged the need for further training on Seretide. The Panel noted that the complainant bore the burden of proof. The Panel had some concerns about the HHBM Seretide training but did not consider that the complainant had demonstrated on the balance of probabilities that the product training was inadequate given the nature of calls likely to be made; no breach of the Code was ruled.

The Panel noted the allegation that IHMs promoted ReQuip XL without any formal training. The Panel noted that the job template for the IHMs which described their key responsibility. IHMs reported into the business manager. GlaxoSmithKline submitted that the IHMs had never promoted ReQuip XL.

The Panel did not consider that the material provided by the complainant in relation to IHMs and ReQuip XL demonstrated that they had any promotional role in relation to ReQuip XL as alleged. An email to the HHBM team referred to IHMs facilitating introductions for an HHBM. The complainant had not established that the IHMs had any promotional role in relation to ReQuip XL and thus there was no requirement that they be trained on it; no breach of the Code was ruled.

The Panel noted that the purpose of the internal presentation to the Revolade head office team entitled 'Smashing targets' was to help the team understand the importance of managed market access and the effect on national targets of small local brand achievements. The Panel did not consider that the title 'Smashing targets' was unethical given the audience and content; no breach of the Code was ruled.

In relation to the email which discussed the names and locations of investigators who had used Revolade under the named patient programme, the Panel noted that it was sent to HHBMs rather than to sales representatives as stated by the complainant. No confidential patient data was disclosed. A funding issue had arisen and thus the HHBMs were to discuss ongoing funding with budget holders at the relevant hospitals. The complainant had referred to this email but did not state why it was unacceptable under the Code. The Panel noted that the complainant had not established that the email in question was unacceptable and thus ruled no breach of the Code.

The Panel noted that it had asked GlaxoSmithKline to respond to Clause 2 on this point and noting its no breach rulings above consequently ruled no breach of Clause 2.

A GlaxoSmithKline UK Limited employee complained about the promotion of and/or staff training on Revolade (eltrombopag), Seretide (fluticasone/salmeterol) and ReQuip XL (ropinirole). Both before the initial response was received and subsequent to that response, further allegations were made.

When responding to the complaint the Authority asked GlaxoSmithKline to bear in mind Clauses 2, 3.2, 9.1, 15.1, 15.2 and in addition, in relation to point B3, Clause 15.9 of the Code.

A Alleged off-licence promotion of Revolade

1 Email sent by a representative

COMPLAINT

The complainant alleged that GlaxoSmithKline had promoted the use of Revolade outside its current licensed indication for immune (idiopathic) thrombocytopenic purpura (ITP). The complainant provided a copy of an email which he/she alleged showed that a representative had promoted the use of Revolade via an individual funding request (IFR) for myeloid fibrosis.

RESPONSE

GlaxoSmithKline stated that Revolade, according to its summary of product characteristics (SPC), was indicated for adult chronic ITP in splenectomised patients refractory to other treatments (eg corticosteroids, immunoglobulins). Revolade might be considered as second line treatment for adult non-splenectomised patients where surgery was contraindicated.

As Revolade was not recommended by the National Institute for health and Clinical Excellence (NICE) for use within its marketing authorization, primary care trusts (PCTs) would not routinely fund it and so clinicians who wished to use it would have to raise an IFR.

An email from a GlaxoSmithKline representative to a hospital consultant was provided by the complainant. The representative was a very experienced representative with many years in the pharmaceutical industry during which his/her conduct had never been questioned. He/she had been trained on the licensed indication for Revolade and on chronic ITP.

GlaxoSmithKline explained that the representative had delivered a presentation on Revolade at a hospital meeting and let it be known that GlaxoSmithKline had an approved document that contained on-licence clinical data to support clinicians when completing a form to request funding for Revolade on an individual patient basis. After the meeting a consultant asked the representative for information on Revolade to use to support a funding request for one of his patients with chronic ITP. The patient also had myelofibrosis and the consultant requested information on myelodysplastic syndrome (MDS) and bone marrow failure syndromes (of which myelofibrosis was one). The representative referred this unsolicited request to the medical team to follow up. The consultant asked the representative to arrange an appointment to discuss the GlaxoSmithKline IFR materials. When the representative contacted the consultant's secretary, he/she was asked to email the consultant directly for an appointment. By way of a reminder, the representative referred to the patient as having 'myeloid fibrosis'. The representative met the consultant to discuss an IFR for use of Revolade in chronic ITP, using the approved materials. Only data relating to chronic ITP was discussed. The case details of the patient in question were not discussed.

GlaxoSmithKline had contacted the consultant for corroborating information, but had not received any information to date, but a signed statement from the representative explaining the context of the email was provided.

GlaxoSmithKline therefore submitted that the evidence indicated that the representative did not promote Revolade out of licence.

PANEL RULING

The Panel noted that the subject matter of the email at issue read 'Request for an appointment re an IFr submission for a patient with Myeloid Firosis [*sic*]'. The email referred to a telephone conversation with the consultant's secretary and suggested dates for an appointment to 'discuss putting together the IFR for your patient with Myeloid Fibrosis'. The email in question was sent by the representative to the consultant at the request of his secretary.

The Panel noted the licensed indication for Revolade. The Panel also noted that according to GlaxoSmithKline, the consultant had, after a hospital meeting about Revolade, asked the representative for information about Revolade to support a funding request for a patient with chronic ITP as the patient had myelofibrosis and asked for information about MDS and bone marrow failure syndrome. The representative ensured that the latter request was satisfied via GlaxoSmithKline's medical information function.

The Panel noted that whilst the subsequent meeting discussed an IFR for the use of Revolade in chronic ITP using approved materials, the subject matter of the email in question referred to myeloid fibrosis as the representative had considered that this was the only way to identify the reason for the meeting. The Panel queried whether this was so. In his/her signed statement the representative acknowledged that the email could have been misconstrued and that during the subsequent meeting the consultant had the patient in mind but the representative had stressed that they could only talk about the use of Revolade in chronic ITP.

Whilst the email did not expressly refer to Revolade, it was an integral part of a series of communications about the medicine. The IFR referred to in the subject matter of the email was in relation to Revolade. The Panel considered that whilst there was no evidence that the subsequent meeting was unacceptable in relation to the requirements of the Code, the subject matter of the email in question implied that the IFR related to Revolade and its use in myeloid fibrosis and consequently promoted Revolade outside of its licensed indication as alleged. A breach of Clause 3.2 was ruled.

The Panel considered that the representative should have been mindful of the impression given by the subject matter of the email and noted the representative's acknowledgement that it could have been misconstrued. High standards had not been maintained in this regard by the representative and a breach of Clause 15.2 was ruled. There was no evidence that the company had failed to maintain high standards and the Panel ruled no breach of Clause 9.1 and consequently no breach of Clause 2.

2 Tactical brand plan

The complainant provided a copy of an internal email written in August 2010, from an HHBM, to two GlaxoSmithKline employees, entitled 'Brand Plan Global: Revolade reading only' which reproduced the outputs of the UK brand plan day and attached a copy of the global tactical brand plan.

COMPLAINT

The complainant alleged that, *inter alia*, the tactical brand plan for Revolade led representatives to promote the product for unlicensed indications.

RESPONSE

GlaxoSmithKline submitted that the 'Revolade ITP Annual Brand Plan 2011' was an internal, above-country document which outlined the life cycle strategy for Revolade for 2011 and beyond in Europe, Asia-Pacific, Japan and the emerging markets and was provided as reference material for local operating companies to develop their local brand plan.

This document was for internal planning purposes and was used by the brand planning team to create the UK plan taking the UK marketing authorization and other local requirements into account. The brand planning team consisted of a number of aligned individuals one of whom was also the author of the email in question.

The brand plan was sent as an attachment to two employees as background reading as one employee required information on brand strategy following a period of sick leave. The other employee was copied

in as he/she was the trainer helping the first employee with some refresher training and he/she was new to the brand.

The rest of the email contained brainstorming ideas from an internal meeting set up to create ideas for commercial and marketing activities as well as medical and data generation activities. The only reference to an off-licence indication was the line 'Explore data to cover use in presurgery – off license but reported to the team' under the heading 'KEG' (key evidence generation) which was a medical strategy for clinical trials and data generation.

Neither the global brand plan nor the email contained any information that suggested plans for off-licence promotion.

In addition GlaxoSmithKline provided certified archived materials to show that representatives were comprehensively trained on the Revolade SPC and that all training was consistent with the marketing authorization. In addition, representatives were trained in the company's procedure to deal with unsolicited requests for off-licence information.

In response to a request for further information GlaxoSmithKline confirmed that the employee, who required training, was a member of the HHBM team.

HHBMs were a field based team working in secondary care with senior non-clinical NHS staff; they acted as a link to GlaxoSmithKline as account managers (an explanatory slide set of their role was provided). They were only expected to have a basic knowledge of GlaxoSmithKline medicines. Their conversations were centred on local access to medicines and budget management and they sought insight into the local health economies in relation to GlaxoSmithKline medicines. They had access to representatives and other in-house experts who could be called upon to discuss GlaxoSmithKline medicines and their use. They could also offer additional support to specific brands by having discussions with payer customers.

The email in question contained the outputs/minutes of an internal brand planning meeting. An excerpt from the author's witness statement was reproduced. As the minutes were shared in their entirety, there was reference to the medical affairs part of the brand plan. As stated above, the only reference to off-licence use was the line 'Explore data to cover use in presurgery – off license but reported to the team' under the heading 'KEG' (key evidence generation) which was a medical strategy for clinical trials and data generation. As this off-licence use had been reported to the brand team, the medical department would have to explore further in order to produce medical information responses as well as explore possibilities for data generation in clinical trials. As this was clearly a medical department issue, no further qualification was needed and no follow up with the email recipients would have been necessary.

The author of the email in question stated in his/her witness statement,

> 'I have not received training for off licence use or future indications. I have never seen any literature about this. In the early marketing materials used for in approved Advanced Planning Information in Sept 2009, I think it was generically mentioned under other ongoing trials discussed that there may be more indications/further research, maybe hepatitis, but it was anticipated this would never happen so we were told we shouldn't talk about it.'
>
> 'I never felt asked or encouraged to discuss off licence ... colleagues have never done this.'

GlaxoSmithKline stated that in its follow-up with the trainer who received the email, he/she could not recall the discussions following the email; however he/she had confirmed that any training for individuals would only use approved materials and follow the same format and agenda as for a wider group.

PANEL RULING

The Panel noted that the Revolade tactical brand plan and covering email were provided in response to a request for background brand strategy information from a GlaxoSmithKline trainer to satisfy the training needs of an HHBM. The author of the email in question was an individual who was aligned to the brand planning team.

The covering email explained that the global tactical brand plan was for background use only and that a UK brand plan would be produced subsequently. The email outlined six outputs from a UK brand plan day including 'Clinical Experience and KEG [Key Evidence Generation] Explore data to cover use in presurgery - off license but reported to team'. The Panel noted that it had to consider whether the provision of the global tactical brand plan and covering email to the HHBM (who was not a member of the brand team) encouraged the promotion of Revolade beyond its licence.

According to GlaxoSmithKline HHBMs worked with senior non-clinical NHS staff on local access to medicines and budget management; they were only expected to have a basic knowledge of GlaxoSmithKline medicines. They could offer support to specific brands by having discussions with payer customers. The role of the HHBMs was further described in an internal presentation (UK/PPM/0158/11) as, *inter alia*, driving the 'growth of GlaxoSmithKline brands through excellent account management in secondary care', and at the launch of the product they would 'lead and support the account team to drive rapid uptake of the brand, including plans for formulary inclusion'. Reference was made to subsequent commercialisation. Key contacts for most HHBMs included senior pharmacists.

The Panel noted that the first slide of the Revolade global tactical brand plan made it clear that all materials were subject to local review and approval. The plan discussed the disease, global market access challenges, growth strategies and performance measurement etc. There was no reference to off-licence use. The Panel did not consider that the

provision of the global tactical brand plan to the HHBM was contrary to the Code as alleged; it did not discuss unlicensed use of Revolade and the covering email made it clear that it was provided for background reading only. GlaxoSmithKline had not been asked to respond to Clause 15.9 on this point. The Panel did not consider that there had been a failure to maintain high standards in relation to the content of the global tactical brand and its provision to an HHBM; no breach of Clause 9.1 was ruled.

The Panel noted that the subject of the covering email was 'Brand Plan Global: Revolade reading only: [name]'. A bullet point in the email read 'Explore data to cover use in presurgery – off licence but reported to the team'. GlaxoSmithKline explained that as this off-licence use had been reported to the brand team, its medical department would explore data generation and medical information responses. The Panel considered that the email did not make this clear and without the benefit of GlaxoSmithKline's explanation the bullet point in question was open to misinterpretation by field based staff who did not participate in the meeting. The Panel therefore did not accept GlaxoSmithKline's submission that as it was a medical department issue, no further qualification was needed and no follow up with the email recipients would have been necessary. The outputs of the meeting had been disseminated beyond the UK brand plan team to, *inter alia*, a member of a field based team without the benefit of GlaxoSmithKline's detailed explanation. The covering email, including the subject title, made it clear that the global brand plan was for background only but no such qualification was applied to the outputs of the UK brand planning meeting.

The Panel was concerned about the unqualified reproduction of the outputs from the UK brand meeting in the covering email which referred to the unlicensed use of Revolade and its provision to an HHBM who was not a member of the UK brand planning team. The Panel considered that the dissemination of such material to an HHBM who, *inter alia*, would have product related discussions with payer customers, would have to comply with the Code. The trainer to whom the email was also sent could not recall discussions following the email but had confirmed that approved materials were used for all subsequent training for the HHBM. The Panel noted that GlaxoSmithKline had not been asked to respond in relation to Clause 15.9 which covered representatives' briefing material in relation to this allegation. The Panel considered that the unqualified reference to unlicensed use in the email in question together with its provision to an HHBM who was not a member of the UK brand planning team meant that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such; no breach of Clause 2 was thus ruled.

B Training

1 Seretide product knowledge test

COMPLAINT

The complainant alleged that in November 2011 a team of hospital business managers falsified a Seretide product certification examination. All of the managers sat the product knowledge test at the same time and the answers were read out by a team member as instructed by the team line manager. This deliberate action, following limited training, meant that the hospital business managers were not adequately trained on Seretide when they engaged with customers.

RESPONSE

GlaxoSmithKline stated that the HHBMs were a field based team that worked in secondary care with senior non-clinical NHS staff and acted as a link to GlaxoSmithKline as account managers. They could be involved in advance planning notification, share knowledge of business processes and discuss formularies. They were only expected to have a basic knowledge of GlaxoSmithKline medicines but had access to representatives and other in-house experts who could be called upon to discuss GlaxoSmithKline medicines and their use. They could also offer additional support to specific brands by having discussions with payer customers. When this was required, the HHBMs underwent product training which contained elements of the training programme for representatives, but was not as comprehensive.

Seretide was an important brand for GlaxoSmithKline and due to the changing NHS environment there was the possibility that the HHBMs might have to discuss Seretide with senior managers and payers. The team manager decided that they would benefit from some basic training on the brand. As they were not routinely trained on Seretide one of the team was asked to pull together a programme consisting of a series of online materials, modules, background reading and webinars with experts in the company. To finish the training and consolidate knowledge, a quiz was put together which used questions from the Seretide test for representatives. The quiz took place in November 2011 during a team meeting.

GlaxoSmithKline submitted that as part of its thorough investigation it interviewed, with minimal warning, the five people involved on the day. None of the five signed responses detailing events on the day supported the complainant's allegations that answers were read out or that the quiz was falsified. HHBMs frequently received relevant training on products and account management. In 2011 they received 20 days' training of which 13 days were product training. As they were not product specialists, this training provided them with knowledge above and beyond that required for their role.

Based on the evidence above, GlaxoSmithKline strongly refuted the allegation that the quiz was conducted inappropriately and that the HHBMs were not adequately trained.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request for comments on GlaxoSmithKline's response, the complainant provided copies of emails and other documents which he/she considered showed that HHBMs had actively promoted Seretide before they had been trained and undertaken the test. The complainant stated that it was therefore clear that HHBMs had promoted Seretide to NHS colleagues and had been targeted by their manager as shown in the personal development plan (PDP) before they had been formally trained and certified as 'customer safe' in their product test. The complainant considered that this was unacceptable and in breach of the Code as promotion had taken place as shown in documents provided. The complainant confirmed that he/she was in the room on the day and the answers were read out by an HHBM under the guidance of a manager. The complainant was not surprised by the response of fellow colleagues and suggested they were briefed by telephone before the investigation and interviews took place, despite GlaxoSmithKline's response. As the HHBMs had to log in to GlaxoSmithKline's on-line learning platform to undertake the test then GlaxoSmithKline's electronic records would show that all HHBMs were logged on at the same time. In addition, the test results would also show that every HHBM got the price of the dose of Seretide wrong in the test as this was the price that was provided as part of the pre-reading for the test. Indeed further evidence of this would be found in the same email sent by the training department to every HHBM correcting them on the actual price after the test had taken place.

FURTHER COMMENTS FROM GLAXOSMITHKLINE

In response to a request for further information, GlaxoSmithKline reiterated that it believed that both HHBMs and sales representatives received comprehensive and appropriate training and that the depth and breadth of this training was evident from the enclosures provided with its response above. As outlined above, the HHBM role was different from that of a product representative; the training they received reflected this.

The assessment in question was an informal end-of-training quiz, the purpose of which was knowledge consolidation and not knowledge evaluation.

As previously stated, the HHBMs were not product experts and were not expected to have clinical conversations. Representatives' training courses ended in an invigilated examination with a pass mark of 90% to ensure that their knowledge met the high standards required.

If clinical or medicine related conversations were required then HHBMs were able to draw upon appropriately trained representatives to do this.

PANEL RULING

The Panel noted that GlaxoSmithKline had been asked to respond, *inter alia*, in relation to Clause 15.1 of the Code which applied to representatives and in this regard the Panel firstly had to consider whether the HHBMs satisfied the definition of a representative under the Code. GlaxoSmithKline had submitted that HHBMs did not promote medicines. The Code defined a representative in Clause 1.6 as anyone calling on members of the health professions and administrative staff in relation to the promotion of medicines. This was a wide definition and could cover the activities of those employees that companies might not call or consider as representatives.

Clause 1.2 defined promotion as 'any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines'.

The Panel noted GlaxoSmithKline's submission that the HHBMs worked with senior non-clinical NHS staff on, *inter alia*, formularies. They could also offer additional support to specific brands by having discussions with senior managers and payers for which they underwent product training as there was a possibility that HHBMs would be required to have discussions with senior managers and payers and the training event in question was designed to satisfy this additional training need in relation to Seretide. The Panel noted that the PDPs provided referred primarily to a facilitation and account mapping role in relation to Seretide.

The Panel examined the HHBM presentation, 'Hospital Healthcare Business Managers – supporting access to medicines', which outlined the HHBM role. Its overall objective was to 'drive the growth of GlaxoSmithKline brands through excellent account management in secondary care'. Pre-launch, launch and post-launch functions were described. Accelerating formulary inclusion and expanding product use; facilitating managed entry and market access were mentioned. The HHBM team had experience in designing and delivering formulary submission business cases to business managers, senior clinicians, commissioners and pharmacists. A slide headed 'Where do we fit into the account team?' listed senior pharmacists and drug and therapeutic committee (DTC)/formulary committee and senior trust directors as amongst the HHBMs' customers.

The Panel noted GlaxoSmithKline's submission that HHBMs could offer additional support to specific brands by having discussions with payer customers. In this regard the Panel also noted that a document provided by the complainant entitled 'The role of the HHBM within the Respiratory Market Access' stated that within specific accounts identified by the area business manager (ABM) the HHBM would proactively raise Seretide to discuss the current situation. The Panel noted the HHBMs' broad role as set out in the papers provided by both parties. The Panel noted the definitions of promotion and representative in the Code as set out above and considered that merely because HHBMs did not interact with prescribers did not mean that such interactions were not promotional as defined in the Code. The Panel considered that a limited aspect of the HHBMs' role was likely to involve discussion of

specific medicines and taking all the circumstances into account, the Panel considered that, in relation to this part of their role, they acted as representatives as set out in the Code.

The Panel noted that the parties' accounts of the training event in November differed. It was difficult to determine precisely what had occurred. The Panel noted that the complainant bore the burden of proving his/her complaint on the balance of probabilities. The complainant alleged that it was not a *bona fide* training event and the answers were read out to participants. GlaxoSmithKline explained that it was a knowledge consolidation event rather than evaluation, at the end of an online product training course. The Panel noted that according to the unsigned witness statements provided by GlaxoSmithKline whilst at least one participant completed the test alone, the majority appeared to have completed the informal test collaboratively, with the benefit of discussion.

The Panel noted that Clause 15.1 required representatives to be given adequate training and have sufficient knowledge to enable them to provide full and accurate information about the medicines which they promoted. The Panel considered that it was acceptable to run informal training sessions to consolidate rather than evaluate participants' product knowledge as described by GlaxoSmithKline. However, the overall training package must satisfy the relevant requirements of the Code. The complaint on this point related solely to the training event at issue. The Panel noted GlaxoSmithKline's submission that further extensive training was provided to HHBMs. The Panel did not consider that the conduct of the training event in question was such that the company had failed to satisfy the broader product training requirements of Clause 15.1 as alleged. No breach of Clause 15.1 was ruled. The company had not failed to maintain high standards in relation to the event; no breach of Clause 9.1 was ruled. The Panel consequently ruled no breach of Clause 2.

2 Product knowledge review

COMPLAINT

The complainant alleged that in November 2011 at GlaxoSmithKline's UK head office, GlaxoSmithKline employees falsified their annual product certification examination to ensure compliance with the Code. The team, directed by a manager, had received from him/her and the team trainer repeated text messages in the preceding weeks which set out the questions and answers within the examination. The team sat the examination at the same time and the answers were read out by a manager. This deliberate action meant that given the nature of their cross portfolio role, the HHBMs were not trained to a standard that allowed them to have accurate discussions with customers.

RESPONSE

GlaxoSmithKline considered that the complainant's reference to an 'annual product certification examination' was to the product knowledge review process used to ensure that representatives continued to have excellent knowledge relevant to the therapy area and products they promoted.

Although HHBMs were not product specialists and did not require formal product knowledge review, in 2011 it was decided to pilot with them this format of knowledge review. Questions for the pilot were selected from a bank of questions used for representatives, including some NHS environment questions. Participants could have three attempts to pass the test with the opportunity to review incorrect answers. A pass mark of 90% or more was required. Some coaching questions were sent by text message in the preceding weeks to indicate the types of questions likely to be asked and provide guidance for revision. The pilot took place in November 2011.

GlaxoSmithKline submitted that in its thorough investigation, it interviewed, with minimal warning, five people involved on the day. These interviews could be considered to be individual responses and indicated that three questions were received by text as prompts, however no answers were provided. In addition, all interviewees refuted the allegation that answers were read out.

GlaxoSmithKline submitted that the HHBMs were adequately trained for their role. The decision to pilot an annual test was part of its drive for the highest possible standards; the learnings from this pilot would be incorporated into a tailored future training plan.

GlaxoSmithKline submitted that it had not discovered any evidence to support any of the allegations and therefore it denied any breach of the Code.

GlaxoSmithKline invested heavily in the training of its employees; there were over 50 people in the commercial training and development team in the UK.

GlaxoSmithKline considered that it took its business very seriously and ensured that employees were equipped to the highest standards to perform their roles whoever they were. GlaxoSmithKline also believed that its culture understood the importance of upholding its high ethical values. A survey in late 2009 showed that the vast majority of employees understood what constituted ethical business practice and conduct in their job; considered that their working environment encouraged ethical behaviour even in the face of pressures to meet business objectives and that leaders in their departments created an atmosphere of trust in which concerns could be raised.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant refuted GlaxoSmithKline's suggestion that this was a pilot as the entire company was subject to annual product certification and this was not done by HHBMs in the past but as the IHMs had to undertake the test then it was considered that the HHBMs should also be certified in 2011. The complainant had never seen a document saying it was a pilot and did not believe it existed. The questions and answers were produced by GlaxoSmithKline's

head office by an employee who had also selected the questions for the IHMs. This bank of questions was sent to the relevant manager and it was first shown to the HHBMs at a team meeting in September 2011. It was decided at the meeting that a series of questions would be sent by text messages as sending them by email would be suspicious. An HHBM undertook this task and whilst he/she was on annual leave a manager sent texts via the company text system as well. The complainant refuted that just three texts were sent as he/she received far more than that and he/she was sure his/her fellow colleagues did too. The complainant suggested that GlaxoSmithKline provide the telephone records of the HHBM sending the questions by text as this would demonstrate that many more than three texts were sent out and the GlaxoSmithKline text system would also show the manager sent messages via this route. The team undertook the test using the company's on-line learning platform and once again GlaxoSmithKline's electronic records would show that almost everyone scored the same as the answers were read out. However, one HHBM sat a different set of test questions and just passed the test but he/she was helped extensively by the manager and fellow HHBMs after they had finished their test. The complainant submitted that many of the questions in the test, particularly around the NHS, were very difficult and that he/she had never received any formal training on the subject matter examined in this test. The complainant knew that without the answers he/she would not have passed the examination and he/she was sure almost all other HHBMs would have failed had the answers not been read out.

FURTHER COMMENTS FROM GLAXOSMITHKLINE

In response to a request from the Panel for further information, GlaxoSmithKline submitted that the annual review process was piloted with the HHBMs' role for the first time in November 2011. The process had been carried out successfully over a number of years with representatives to test their level of product knowledge. The test was computer based; each individual completed it online whilst in a room together and the results were recorded electronically. The bank of questions was presented to each individual in a random order which meant that at any one time individuals completed different questions from the bank in a different order. There was the opportunity to sit the test three times if the required pass mark was not reached. If a pass was still not achieved, a period 'off the road' and retraining was conducted (frequently asked questions were provided).

The results report from this test showed a range of final scores which suggested that this was not a result of collaboration (a copy was provided). The time taken to complete the tests was also shown; again there was a range. The HHBM who sat a different test had a bespoke set of questions to reflect the regional health economies that he/she covered (a copy was provided).

In addition, the signed witness statements consistently refuted the allegations regarding the conduct of individuals on the day. Any learnings from this pilot would be incorporated when the annual test was officially rolled out. GlaxoSmithKline was confident that it had properly evaluated the knowledge of both the HHBM team and its representatives.

There were 30 questions in total in the bank of sample questions with product questions taken from the much larger bank of questions in the representatives' training programmes. No answers were sent out. The aim of the text was to stimulate individual revision and learning ahead of the annual review amongst a field based team.

GlaxoSmithKline believed that HHBMs were adequately trained for their role. The annual test was piloted as part of the company's drive for the highest possible standards; the learnings from this pilot would be incorporated into a tailored future training plan.

GlaxoSmithKline took its business very seriously and ensured that its employees were equipped to the highest standards to perform their roles, whoever they were. It had a culture that understood the importance of upholding its high ethical values.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant strongly argued that there was evidence to suggest that the Code had been breached. The complainant also noted that people had been dishonest in their responses to these matters, which was astonishing given that GlaxoSmithKline's electronic records would show this to be the case particularly with regard to the two examinations undertaken in November 2011.

The complainant stated that he/she was present during the tests and the meetings and found it disturbing that GlaxoSmithKline had managed to engineer fictitious responses to these allegations from his/her colleagues. This demonstrated the cover up attitude that existed when GlaxoSmithKline did not like the behaviour of its employees as seen before when other failures had come to light.

PANEL RULING

The Panel noted that the complaint concerned the conduct of the pilot annual product knowledge review which took place in November 2011. The Panel noted its comments above at point B1 about the role and status of HHBMs and considered that they applied here.

The Panel noted that, once again, the parties' accounts differed and it was difficult in such circumstances to determine precisely what had occurred. The Panel noted that the complainant bore the burden of proving his/her complaint on the balance of probabilities.

The Panel noted GlaxoSmithKline's submission that the annual review process was first piloted with the HHBMs in November 2011. The process had been carried out successfully over a number of years with representatives to test their level of product knowledge.

The Panel noted that GlaxoSmithKline had provided a number of unsigned witness statements from HHBMs who took part in the pilot test. All interviewees refuted the allegation that answers were read out as alleged. The witness statement of a manager explained that on the day of the test he/she decided to run it as an open book test with access to online information for participants. Some participants were helped to think about where to look online. The test was described as a knowledge and information seeking test to see how they got on. It was acknowledged that this activity needed to be run differently next time.

The Panel considered that in principle it was acceptable to run pilot training sessions to inform and improve the overall product training package. However, the overall training package should comply with the Code. The complaint on this point related solely to the training event at issue. The Panel noted GlaxoSmithKline's submission that further extensive training was provided to HHBMs. The Panel did not consider that the conduct of the training event in November demonstrated that the company had failed to satisfy the broader product training requirements of Clause 15.1. No breach of Clause 15.1 was ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2.

3 Promotional practice and training

COMPLAINT

The complainant's stated that in his/her view, GlaxoSmithKline's overall product training standards were below that expected by the Code, it was acceptable in some teams and roles to just 'get through' the necessary examinations and this might be a more widespread company issue.

The complainant subsequently submitted further documents about the promotional practices and representatives' training at GlaxoSmithKline. The material mainly concerned the promotion of GlaxoSmithKline's medicines to NHS customers by representatives who had not received formal and certified internal training. The complainant provided emails and PDPs as well as other documents which he/she considered showed that the knowledge of, and support for, this practice was widespread across many roles and levels within GlaxoSmithKline. Some key performance targets for people appeared in their development plans and activities before they were trained on the product. The complainant noted, for example, that the HHBM team were only formally trained on Seretide in November 2011, yet the untrained team actively promoted the product to NHS customers, as encouraged by their line manager and business unit directors, in 2010.

The complainant subsequently provided new documents about the promotion of ReQuip XL using IHMs, although those IHMs had never received any formal training internally. The complainant provided a copy of a presentation by a manager to the Revolade marketing team which he/she found wholly unethical as it was entitled 'Revolade Smashing targets'. The complainant referred to an email from the Revolade marketing team to the representatives that revealed the locations and names of doctors using Revolade under the Named Patient Programme.

In response to a request for comments on GlaxoSmithKline's initial response, the complainant reiterated that the standards of training at GlaxoSmithKline were below standard. He/she could list and provide many more examples of where he/she had been in customer calls with representatives who clearly should not have been allowed to promote medicines as they did not have the necessary knowledge to accurately present product information. The complainant did not consider that it was acceptable or ethical; NHS colleagues expected pharmaceutical company employees engaged in discussions about a medicine to have a minimum standard of training and knowledge to provide evidence based information accurately. The complainant considered it was not sufficient to state that HHBMs only had basic product knowledge. The complainant also considered that a customer having granted an HHBM time for an interaction would think it was unacceptable for that person each time to organise for another representative or other GlaxoSmithKline expert to come back with the answer.

It was also difficult to argue that promotion had not taken place when clearly documents and emails showed people had engaged with customers almost a year before receiving certification, a clear breach of the Code.

The complainant understood why GlaxoSmithKline would wish to refute these allegations as it was a failure on its part in this regard. It must also be particularly difficult when GlaxoSmithKline portrayed itself as conducting business in an ethical manner yet within it things were markedly different to the image portrayed. The complainant stood by his/her complaints.

In addition to the Clauses previously cited, GlaxoSmithKline was also asked to respond in relation to Clause 15.9.

GlaxoSmithKline noted that the complainant had raised further allegations about the promotional practice and training of representatives, the promotion of Seretide, ReQuip XL and Revolade and again, the conduct of a manager. Both the original and the additional complaint had resulted in thorough internal investigations and on this basis GlaxoSmithKline continued to strongly refute these allegations.

GlaxoSmithKline noted that the further allegations from the complainant resulted from two emails; one sent in early February 2012 and one in late February 2012.

FURTHER COMMENTS FROM THE COMPLAINANT

In this email the complainant stated 'The documents attached are mainly concerning the promotion of GSK medicines to NHS customers without those

representatives having received formal and certificated training internally. I enclose emails and PDPs as well as other documents showing that the knowledge of this practice and the support for this practice is widespread across many roles and levels within GSK. Some key performance targets for people appear in their development plans and activities prior to them being trained on the product. It should be noted for example that the HHBM team only received formal training for Seretide in November 2011, yet the team actively engaged with NHS customers in promotion without training as encouraged by their line manager and business unit directors in 2010' [*sic*].

RESPONSE

GlaxoSmithKline stated that it invested heavily in the training of its employees; over 50 people were in its commercial training and development team in the UK. Sales representatives were thoroughly and comprehensively trained on Seretide (the agenda and copies of the training slides were provided). They also underwent an annual product knowledge review to ensure that they had sufficient scientific knowledge to enable them to provide full and accurate information.

The complainant specifically referred to the HHBMs which, as stated above, were a field based, secondary care team which worked with senior non-clinical NHS staff and acted as a link to GlaxoSmithKline as account managers. They were only expected to have a basic knowledge of GlaxoSmithKline medicines but had access to representatives and other in-house experts who could be called upon to discuss GlaxoSmithKline medicines and their use. They could also offer additional support to specific brands by having discussions with payer customers. When this was required, they underwent product training which contained elements of the representatives' training programme but was not as comprehensive. HHBMs were not product specialists and were adequately trained for their role.

In 2011 HHBMs received 20 days' training of which 13 were product training. As they were not product specialists, this training provided them with knowledge above and beyond that required by their role.

GlaxoSmithKline strongly refuted the allegation that representatives did not receive formal training and the evidence showed that representatives underwent a thorough formal training programme for Seretide. GlaxoSmithKline stated that the allegation that employees engaged in promotion without training was unfounded.

A number of materials were provided by the complainant as follows:

1 Email from a manager, April 2011

This email was entitled 'The role of the HHBM within Respiratory Market Access 2011' and had an attachment of the same name.

A manager had written an email to clarify that if, during the course of their work, HHBMs obtained information that was relevant to the Seretide brand, then they would refer this to the appropriate individual within the company. They were informed that they were not to have proactive discussions about this brand and, as discussed above, this email predated the Seretide training for HHBMs that took place later in the year. This was made clear in the email where it stated 'The HHBM will NOT proactively raise Seretide or respiratory with a customer unless this has been specifically contracted between the ABM and the HHBM'.

The attachment to the email supported this and showed that HHBMs could be consulted about market access or facilitate introduction of the appropriate role (eg representative). This was clearly stated in the material provided under point 3 of 'the HHBM role' – 'Following identification of an opportunity or threat the HHBM will facilitate the appropriate intervention eg introduction of IHM/HOC [health outcomes consultant]/TS [sales representative] as required'. In the specific circumstance where an HHBM was contracted to proactively discuss the financial implications of Seretide with a budget holder or payor, a basic knowledge level was required (SPC, preparations and prices) as outlined in the document.

GlaxoSmithKline believed that HHBMs were adequately trained for their role. The email supplied reinforced that for areas out of scope they called on resources and acted as facilitator for appropriate roles in the organisation.

2 A manager's Performance & Development Plan (PDP)

This document outlined performance and behavioural objectives for 2011.

The performance objectives were related to the role of the HHBMs as outlined previously.

The complainant specifically referred to Seretide and the fact that HHBMs did not receive product training until late 2011. It clearly stated in the PDP that Seretide support was 'Mainly focused on providing insight and providing specific support in agreed targeted units'.

Specifically with regard to Seretide, the HHBMs were tasked to provide insight where applicable. As stated above, they were clearly steered not to have proactive conversations about this product, and if there were specific circumstances where they would, they were required to have a minimum level of knowledge and facilitate introduction of the appropriately trained representative.

3 Email about an HHBM meeting

This email outlined the agenda for an HHBM team meeting, in June 2011. The agenda clearly showed a full day business meeting to discuss the business environment and propose training for the team. GlaxoSmithKline submitted that there was nothing in this email to support any of the allegations made.

4 NHS budget email to HHBM team in December 2010

This email had the subject 'BMJ Getting better value from the NHS drug budget – guess what's at the top of the list?' and a copy of the BMJ 2010 article 'Getting better value from the NHS drug budget' was attached and circulated within the team for interest as it mentioned GlaxoSmithKline products. Again, GlaxoSmithKline submitted that there was nothing in this email to support any of the allegations made. Understanding the financial pressures of the NHS was part of the HHBM role.

5 An HHBMs' PDP in February 2011

The complainant had made allegations regarding Seretide. In this draft document, there was only one reference to Seretide under 'other' where the HHBM was tasked with discussing the role the HHBM could play with this brand. There was no instruction for any externally facing interaction.

As discussed previously, the HHBM role with regards to Seretide in 2011 was to understand the environment (field intelligence) and facilitate introductions with appropriate roles (eg sales representative).

6 Email about role of HHBMs

This email outlined a possible role for HHBMs in intelligence gathering about the local health economy, based on an actual example. No promotion of Seretide took place, it was clearly field intelligence. Where further conversations were to be had, the relevant person was clearly outlined as being the person drafted in to have that conversation.

As discussed previously, the HHBM role with regard to Seretide in 2011 was to understand the environment (field intelligence) and facilitate introductions with appropriate roles (eg sales representatives).

7 Presentation about HHBM's manager

The attachment to this email was a slide set presentation by GlaxoSmithKline's HHBM. It outlined the performance and development plan for the HHBM including working alongside the local team for Seretide.

Seretide was not mentioned under 'HHBM Core Role' on slide 3 and under 'Activity Overview' on slide 6 it was stated 'Further trust agenda by facilitating meeting between GGC/Lanarkshire HB med management and GSK business director with a view to scoping JWIs [joint working initiatives] in respiratory'.

This clearly showed the HHBM's involvement as being one of facilitation.

As discussed previously, the HHBM role with regards to Seretide in 2011 was to understand the environment (field intelligence) and facilitate introductions with appropriate roles (eg business director).

GlaxoSmithKline's investigation showed that sales representatives were comprehensively trained on GlaxoSmithKline products and that the HHBM team did not promote Seretide but gathered field intelligence and facilitated introduction of appropriate GlaxoSmithKline employees in 2011. This was consistent throughout the enclosures provided.

8 Requip and IHMs

GlaxoSmithKline noted the complainant's statement 'I have also enclosed some new documents concerning the promotion of Requip XL using IHMs in GSK, despite those IHMs having never received any formal training internally' [*sic*].

GlaxoSmithKline submitted that the IHMs (job description was provided) did not promote ReQuip XL brand. ReQuip XL sales representatives were comprehensively trained (ReQuip XL training programme was provided). Furthermore, HHBMs were trained to undertake associated activities and their training took place on 13/14 April 2011 (HHBM Training 2011).

The email to HHBM from a manager which forwarded an email with the subject 'FW: ReQuip XL 60% Price Reduction – opportunity for IHM involvement?' clearly outlined the request to make use of existing relationships, introductions and local knowledge. This was clear from where it stated 'Would it be possible for us (the 3 Neurology ABMs) to contact some of your IHMs?' and also 'Could we use an IHM's knowledge of/relationship with a prescribing advisor (or equivalent) to facilitate an introduction for one of the 3 Neurology ABMs'. There was no suggestion whatsoever that IHMs should be involved in the promotion of, or indeed any customer interaction with regard to, ReQuip XL.

IHMs had never promoted ReQuip XL. Roles that were involved in promotion of this brand had received thorough and comprehensive training. GlaxoSmithKline included details of the representatives' comprehensive training programme for ReQuip XL.

The email with the subject 'FW: Requip XL generic entrants information; FYI Only not to be shared with customers' had an email trail that mentioned an updated budget impact model for dopamine agonists that was available to appropriate members of the account team. An attachment 'ReQuip XL & generic entry June 2011' was a slide presentation for internal training purposes on generics and the competitive environment with regards to ReQuip.

GlaxoSmithKline stated that it was difficult to determine what allegation this enclosure supported. HHBMs were trained on ReQuip XL in April 2011 and started using the budget impact model with payor customers after this. When the price changed, the budget impact model was updated. Knowledge of the competitive environment with regard to generics was pertinent to the HHBM role.

9 Revolade presentation

The presentation 'Revolade Smashing targets' was an internal presentation to help the head office oncology team understand the importance of appropriately managed market access. If appropriate budgetary information was provided in a timely manner, the local healthcare economies could plan in advance. Thus when small numbers of patients were prescribed new medicines in a locality, the overall picture in the country 'smashes' its commercial targets.

GlaxoSmithKline submitted that the setting business targets for an overall brand plan and its achievement in a commercial environment was not unethical.

10 Named patient programme

Revolade received a marketing authorization in the EU on 11 March 2010.

An email from a trainer forwarded a list of investigators who had accessed Revolade for patients under a named patient programme prior to marketing authorization. This information was not sent to sales representatives but to HHBMs following a funding issue in a hospital for one of these patients. The HHBMs then had to find the budget holders in the hospitals relevant to this list in order to discuss ongoing funding. No confidential patient information was disclosed.

GlaxoSmithKline submitted that its investigations had not discovered any evidence to support allegations made in January and early/late February 2012 and it was therefore confident that no breach of any of the clauses stated had occurred.

GlaxoSmithKline reiterated that it believed that it took the conduct of its business very seriously and ensured that its employees were equipped to the highest standards to perform their roles whoever they were. GlaxoSmithKline also truly believed that its culture understood the importance of upholding its high ethical values. A survey in late 2009, indicated that the vast majority of employees understood what constituted ethical business practice and conduct in their job; considered that their working environment encouraged ethical behaviour even in the face of pressures to meet business objectives and that leaders in their departments created an atmosphere of trust in which concerns could be raised.

PANEL RULING

The Panel noted the extensive documentation provided by both parties. With regard to material provided by the complainant it was not always clear which materials the allegations related to. The complainant referred to both representatives and HHBMs but most of the material supplied by the complainant related to HHBMs. The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities.

The Panel noted GlaxoSmithKline's submission that its representatives were thoroughly and comprehensively trained on Seretide. Training slides and other relevant material were provided. The complainant had provided no material in support of his/her allegation on this point. The Panel considered that on the material before it there was no evidence to demonstrate that GlaxoSmithKline's sales representatives were not given adequate training and sufficient scientific knowledge to enable them to provide full and accurate information about the medicines they promoted. No breach of Clause 15.1 was ruled.

In relation to HHBMs and Seretide, the Panel noted its comments about the role of the HHBMs at point B1 above. The Panel noted the role of the HHBMs with regard to Seretide as described in the document 'The role of the HHBM within Respiratory Market Access' and discussed at point B1 above which referred to specific circumstances where HHBMs were contracted to proactively discuss Seretide. The Panel noted that neither the document nor its covering email limited such discussion to financial implications as stated by GlaxoSmithKline. The document stated that the knowledge level required for HHBMs generally included 'a basic understanding of Seretide to include the SPC, preparations and prices'. The undated document was circulated to HHBMs in April 2011 and the covering email referred to its previous circulation to HHBMs in February 2011.

The Panel noted GlaxoSmithKline's submission at point B1 that when HHBMs had discussions with payer customers to support specific brands, they underwent product training. The Panel noted GlaxoSmithKline's submission that in 2011 HHBMs received 20 days' of training of which 13 were product training which GlaxoSmithKline considered provided them with knowledge above and beyond that required by their role. The Panel noted that the HHBM training for Seretide in 2011 comprised product training on 20 October and 3 November (neither were full days). In addition, the HHBM team did distance learning for Seretide and brand managers delivered updates at HHBM team meetings. The Panel noted GlaxoSmithKline's submission at points B1 and B2 about the need for further training to enable HHBMs to have more detailed discussions. The Panel noted that GlaxoSmithKline had, in effect, acknowledged the need for further training on Seretide. The Panel noted that the complainant bore the burden of proof. The Panel had some concerns about the HHBM Seretide training but did not consider that the complainant had demonstrated on the balance of probabilities that the product training was inadequate given the nature of calls likely to be made; no breach of Clause 15.1 was ruled.

The Panel noted the allegation that IHMs promoted ReQuip XL without any formal training. GlaxoSmithKline had responded to this point in relation to, *inter alia*, sales representatives and ReQuip XL but the Panel did not consider that it had an allegation on this point in relation to sales representatives and thus made no ruling on this matter. The Panel noted that the job template for the IHMs described their key responsibility as, *inter alia*, leading the production and implementation of locality account plans to deliver commercial objectives via managed entry, market access and

service development/implementation to ensure an optimum environment for the uptake of GlaxoSmithKline medicines both current and future. IHMs reported into the business manager. GlaxoSmithKline submitted that the IHMs had never promoted ReQuip XL.

The Panel did not consider that the material provided by the complainant in relation to IHMs and ReQuip XL demonstrated that they had any promotional role in relation to ReQuip XL as alleged. An email to the HHBM team in January 2011 merely referred to IHMs facilitating introductions for an HHBM. The complainant had not established that the IHMs had any promotional role in relation to ReQuip XL and thus there was no requirement that they be trained on it; no breach of Clause 15.1 was ruled.

The Panel noted that the purpose of the internal presentation to the Revolade head office team entitled 'Smashing targets' was to help the team understand the importance of managed market access and the effect on national targets of small local brand achievements. The Panel did not consider that the title 'Smashing targets' was unethical given the audience and content; no breach of Clause 9.1 was ruled.

In relation to the email in May 2010 which discussed the names and locations of investigators who had used Revolade under the named patient programme, the Panel noted that it was sent to HHBMs rather than to sales representatives as stated by the complainant. Revolade received its marketing authorization on 11 March 2010. No confidential patient data was disclosed. A funding issue had arisen and thus the HHBMs were to discuss ongoing funding with budget holders at the relevant hospitals. The complainant had referred to this email but did not state why it was unacceptable under the Code. The Panel noted that the complainant had not established that the email in question was unacceptable and thus ruled no breach of Clause 15.9 of the Code.

The Panel noted that it had asked GlaxoSmithKline to respond to Clause 2 on this point and noting its no breach rulings above consequently ruled no breach of Clause 2.

Complaint received **25 January 2012**

Case completed **6 September 2012**

CASE AUTH/2496/4/12

ALLERGAN/DIRECTOR v MERZ

Promotion of Xeomin and Bocouture and breach of undertaking

Allergan complained about three advertisements for Xeomin/Bocouture (botulinum neurotoxin type A) issued by Merz. As the complaint involved an alleged breach of undertaking, that part of it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings. Allergan marketed Vistabel/Botox (botulinum neurotoxin type A).

Allergan noted that Merz had used the claims 'Equipotent', 'Equal Potency' and '1:1 Clinical Conversion Ratio' alongside a visual of either a Xeomin or Bocouture vial standing next to a Botox or Vistabel vial. The visual was clearly designed to emphasise a direct 1:1 equivalence/conversion of the two medicines. Some of the material included the phrase 'Clinical studies suggest …'. In addition, less prominently and usually in smaller font, was the Summary of Product Characteristics (SPC) statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'.

Allergan alleged that the claims, along with the supporting visuals, were misleading and presented only part of the information in the Bocouture or Xeomin SPC. The overall message was that the products were equally potent and could be converted 1:1.

Allergan noted that the Bocouture SPC stated:

> **'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.**
>
> **Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency.'**

The Xeomin (50U) SPC stated:

> **'Due to unit differences in the LD50 assay, Xeomin units are specific to Xeomin. Therefore unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.**
>
> **Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1.'**

Whilst, the Xeomin (100 units) SPC stated:

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

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

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

Allergan considered that, in line with the science behind botulinum toxins and over twenty years of regulatory experience, the most prominent and significant statement in the SPCs was that unit doses of the medicines were not interchangeable. This statement was imposed by the Pharmacovigilance Working Party (PhVWP) and in Allergan's view was not 'superseded' by a contradictory statement based upon non-inferiority clinical studies. Non-inferiority studies could not demonstrate equivalence and in that regard Allergan noted the ruling in Case AUTH/2270/10/09 together with Merz's submission in that case that it had no data to support a claim that Xeomin was equivalent to Botox.

Allergan noted that botulinum toxin potency was a laboratory measure and each manufacturer's assay was unique to its own medicine. When Hunt *et al* (2010) assessed the relative potencies of Bocouture and Vistabel using the Allergan assay, the potency of Merz's Bocouture 50U was found to be, on average, 34 units per vial whereas the average potency of Allergan's Vistabel/Botox 50U was as labelled. Conversely, Dressler *et al* (2008), using the Merz assay determined that the potencies of Merz's Xeomin and Allergan's Botox were not statistically different. Allergan submitted that as different products were likely to behave differently in different assays these findings were not contradictory since each company used its own proprietary assay.

Allergan submitted that these observed differences in potency and enzymatic activity supported the non-interchangeability of unit doses of botulinum toxins. The optimum dosage and number of injection sites in the treated muscle should be determined individually for each patient. A titration of the dose should be performed. Physicians should consult the appropriate SPC to obtain product-specific dosage recommendations.

Allergan alleged that the current Merz campaign and claims at issue were inaccurate, misleading, could not be substantiated and were not based on an up-to-date evaluation of all the available evidence. In particular, significant new data (Moers-Carpi *et al*, 2011) was omitted. These new data from a randomised, double blind, equivalence study (n=220) directly challenged the hypothesis that the products were interchangeable at a 1:1 dose ratio. The basis for this study was the investigators' experience of the relative clinical effectiveness of the different

medicines, the differences seen in the different reference LD50 assays and the different available dose ranging data. Allergan considered that this new data, while not inconsistent with the findings of the Merz non-inferiority studies, clearly challenged the basis for claims of equivalence and a 1:1 conversion ratio.

Allergan alleged that the claims by Merz for 'Equipotency' and '1:1 Conversion' between Xeomin/Bocouture and Vistabel/Botox was a source of significant concern. No 'dosing conversion' occurred or should be implied from the non-inferiority studies conducted by Merz. The direct medical impact was that a significant patient safety risk existed with prescribers encouraged to transfer information from one product to another.

Allergan noted that in Case AUTH/2270/10/09 it was ruled that the results of a non-inferiority study could not be used to claim equivalence. Merz's own submission in that case was that it had no data to support a claim that Xeomin was equivalent to Botox which Allergan believed this was still so. Therefore, Allergan alleged that the claims for 'Equipotency' and '1:1 Conversion' between Xeomin/Bocouture and Vistabel/Botox (ie equivalence) were in breach of the undertaking in Case AUTH/2270/10/09.

The detailed response from Merz is given below.

The Panel considered each advertisement separately. With regard to one Bocouture advertisement, inter-company dialogue had been successful and so the Director decided that only the alleged breach of undertaking would be considered.

The Panel noted that the other Bocouture advertisement featured a photograph of vials of Bocouture and Botox side-by-side. Above the vials was the claim in bold, blue font 'In glabellar frown lines, clinical studies suggest Bocouture vs Botox: Equal Potency 1:1 Clinical Conversion Ratio'. This claim and the photograph took up over half of the advertisement. Below the vials was a thick blue horizontal line beneath which was the statement in smaller black font 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'. This statement and the claim for equal potency were referenced to the Bocouture SPC. The claim for a 1:1 clinical conversion ratio was referenced to Sattler *et al* (2010).

The Panel noted that in Section 4.2 of the Bocouture SPC, Posology and method of administration, the first statement in bold type read 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxins'. A similar bold statement also appeared in the Xeomin SPC. The Panel noted the prominence of these statements in the SPCs and considered that although the Bocouture SPC statement had been included in the advertisement at issue, it was given significantly less prominence than the other claims. Given its position below the thick blue line, it appeared to be separate from the main part of the advertisement. The prominence given to this statement in the SPC had not been reflected in the advertisement. The Panel considered that the advertisement was misleading in that regard. A breach of the Code was ruled. This ruling was not appealed.

The Panel noted that the claim '…clinical studies suggest… Equal Potency…' was referenced to the Bocouture SPC. The relevant statement in the SPC stated 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'. The second part of the claim in the advertisement '1:1 Clinical Conversion Ratio', was referenced to Sattler *et al*, a non-inferiority study which had demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin to Vistabel/Botox in the treatment of glabellar frown lines. The Panel noted that it had previously been established that non-inferiority studies could not be used to imply equivalence.

The Panel considered that the overall impression from the advertisement was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, the advertisement encouraged prescribers to consider that the unit doses of Bocouture and Botox were interchangeable. The Panel considered that the advertisement was misleading in that regard. The Panel considered that the impression given by the advertisement could not be substantiated. Breaches of the Code were ruled. These rulings were not appealed.

The Xeomin advertisement featured a photograph of vial of Xeomin and Botox side-by-side with a colon (:) between them. The headline claim read 'Clinical studies suggest Xeomin and Botox are equipotent, with a conversation ratio of 1:1 Xeomin SPC'. Below the photograph of the vials on the left-hand side was the statement 'Always prescribe by brand, unit doses are not interchangeable'. This was referenced to the Xeomin 50U SPC. The headline claim and the statement were in a similar prominent white font on a black background.

The Panel noted that Section 4.2 of the Xeomin 50U SPC stated the following:

> **'Due to unit differences in the LD50 assay, Xeomin units are specific to Xeomin. Therefore unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.**
>
> **Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1'.**

The Panel noted the prominence given to the first statement in the SPC and that the order of the two statements in the SPC had been reversed in the advertisement, which resulted in the claim 'Clinical studies suggest…' being used as the headline to the

advertisement. The Panel considered that the relative emphasis on the two SPC statements had not been reflected in the advertisement. In the Panel's view, the advertisement encouraged prescribers to consider the unit doses of Bocouture and Botox were interchangeable. The Panel considered that the advertisement was misleading in this regard. The Panel considered that the impression given by the advertisement could not be substantiated. Breaches of the Code were ruled. These rulings were not appealed.

With regard to the alleged breach of undertaking, the Panel noted that inter-company dialogue was not a pre-requisite and it thus considered that that aspect of the complaint would be considered in relation to all three advertisements at issue.

The Panel noted that in Case AUTH/2270/10/09, Merz had been ruled in breach of the Code for claiming that Xeomin was 'At least as effective as Botox with a similar safety profile'. The Panel considered that the claim implied possible superiority of Xeomin vs Botox which was not supported by the available data. A breach of the Code was ruled which was upheld on appeal.

Turning to the advertisements at issue, the Panel noted that they referred to Xeomin/Bocouture being 'equipotent' or having 'Equal Potency' to Botox/Vistabel. There was no suggestion that Xeomin/Bocouture might be more potent than Botox/Vistabel. In that regard the Panel did not consider that the advertisements breached the undertaking given in Case AUTH/2270/10/09. No breaches of the Code were ruled including Clause 2.

Upon appeal, the Appeal Board noted that the undertaking in Case AUTH/2270/10/09 related to a claim that not only implied equivalence but also possible superiority; its ruling had been made on both aspects. In the current case, Case AUTH/2496/4/12, Allergan's alleged breach of undertaking, the subject of the appeal, related only to claims of equivalence.

The Appeal Board noted that there was still no data to show whether Xeomin/Bocouture was equivalent to Botox/Vistabel. Now, as when the ruling in Case AUTH/2270/10/09 was made, there were only non-inferiority studies which showed that the medicines were no worse than each other by a clinically acceptable pre-specified margin.

Turning to Case AUTH/2496/4/12, the Appeal Board considered that the Bocouture advertisement which featured the claim 'In glabellar frown lines, clinical studies suggest' followed by 'Bocouture vs Botox:', 'Equal potency' and '1.1 Clinical Conversion Ratio' together with the visual of a vial of each of the medicines side-by-side, implied that the two products were clinically equivalent and that unit for unit they were interchangeable. The Appeal Board considered that although the claim at issue was not the same as that in Case AUTH/2270/10/09, it was sufficiently similar with regard to a claim for 'equivalence' for it to be covered by the undertaking previously given. The Appeal Board thus ruled a breach of the Code. The appeal on this point was successful.

Similarly the Appeal Board considered that the Xeomin advertisement which featured the claim 'Clinical studies suggest Xeomin and Botox are equipotent, with a conversion ratio of 1:1 Xeomin SmPC' together with a visual of a vial of each medicine side-by-side with a colon between them, also implied that the medicines were clinically equivalent and that unit for unit they were interchangeable. The Appeal Board noted its comments above and thus ruled a breach of the Code. The appeal on this point was successful.

The Appeal Board noted that the Bocouture advertisement included the statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin' and the Xeomin advertisement similarly included the statement 'Always prescribe by brand, unit doses are not interchangeable'. These statements were referenced to the respective products' SPCs and in both advertisements they appeared in a less prominent position and smaller font than the claims and visuals that implied clinical equivalence. The Appeal Board considered that implying that the products were clinically equivalent and hence interchangeable was contrary to statements in the SPCs. The Appeal Board considered that this raised possible patient safety concerns.

The Appeal Board considered that as Merz had no data on which to base the implied claims of clinical equivalence, and as it had breached its undertaking and assurance in Case AUTH/2270/10/09, it had failed to maintain high standards and had thus brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled breaches of the Code including Clause 2. The appeal on this point was successful.

Allergan Limited complained about the promotion of Xeomin/Bocouture (botulinum neurotoxin type A) by Merz Pharma UK Ltd. The materials at issue were two Bocouture advertisements (refs 1070/MER/AUG/2011/JH and 1075/BOC/DEC/2011/JH) and a Xeomin advertisement (ref 1281/XEO/OCT/2011/JL). As the complaint involved an alleged breach of undertaking, that part of it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Allergan marketed Vistabel/Botox (botulinum neurotoxin type A).

COMPLAINT

Allergan alleged that the advertisements and overall campaign led prescribers to conclude that Xeomin/Bocouture and Vistabel/Botox were interchangeable in terms of potency units and delivered equivalent clinical results. Allergan considered that this marketing strategy fundamentally contradicted the intent of the Pharmacovigilance Working Party (PhVWP) which, in 2006, mandated that all botulinum toxin summaries

of product characteristics (SPCs) included wording to highlight the non-interchangeability of unit doses between products in order to ensure their safe and appropriate use. Allergan strongly disagreed with Merz's view that the claims were supported by the clinical data, consistent with the SPC and not inconsistent with the findings of the PhVWP, and it thus alleged that the materials were in breach of the Code.

Allergan noted that the claims 'Equipotent', 'Equal Potency' and '1:1 Clinical Conversion Ratio' were used alongside a visual of vials of Xeomin/Bocouture and Botox/Vistabel standing side-by-side. The visual was clearly designed to emphasise a direct 1:1 equivalence/conversion of the two medicines. In some of the promotional materials the phrase 'Clinical studies suggest …' was added. In addition, less prominently and usually in smaller font, was the SPC statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'.

Allergan alleged that the claims, along with the supporting visuals, were misleading and presented only part of the information in the Bocouture or Xeomin SPC. The overall message given to health professionals was that the products were equally potent and could be converted 1:1.

Allergan noted that the Bocouture SPC stated:

> 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.
>
> Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency.'

The Xeomin (50U) SPC stated:

> 'Due to unit differences in the LD50 assay, Xeomin units are specific to Xeomin. Therefore unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.
>
> Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1.'

Whilst, the Xeomin (100U) SPC stated:

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

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

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

Allergan considered that, in line with the science behind botulinum toxins and over twenty years of regulatory experience, the most prominent and most significant statement on the SPCs for all the botulinum toxins was that unit doses of the medicines were not interchangeable. As noted above, this statement of non-interchangeability was imposed on all botulinum toxin manufacturers by the PhVWP; in Allergan's view it was not 'superseded' by a contradictory statement based upon clinical studies of a non inferiority design. Non-inferiority studies could not demonstrate equivalence. Allergan noted the ruling in Case AUTH/2270/10/09 that the results of a non-inferiority study could not be used to claim equivalence and Merz's submission in that case that it had no data to support a claim that Xeomin was equivalent to Botox.

Allergan noted that assessment of potency was a laboratory measure and not a recognised clinical endpoint. Potency was measured in the laboratory using an LD50 assay. Each botulinum toxin manufacturer had its own unique and proprietary potency assay methodology. Data sets from Merz and Allergan in relation to the potency of the competitor products gave contradictory results for reasons which could be explained by the differences in the toxins and the assay methods.

Allergan submitted that Hunt *et al* (2010) assessed the relative potencies of Bocouture 50U and Vistabel 50U using the Allergan standardised potency bioassay (approved and used for quantifying the biological activity of formulated ~900 kD Botox) and evaluated enzymatic activity through LCA-HPLC. The average potency of Bocouture 50U dose was found to be 34 units (31-36 95% CI) per vial vs 50 units (46-56 95% CI) per vial for Vistabel/Botox (ie as labelled). Potency was verified by running four separate test sessions for both medicines. These results were further corroborated with a lower than expected light chain activity for Bocouture and were consistent with previous findings for Xeomin 100U. Conversely Dressler *et al* (2008) determined the biological potencies of five commercially available unexpired batches of Xeomin and Botox using the LD50 bioassay for batch release of Xeomin and concluded that the potencies of the Xeomin and Botox batches were not statistically different.

The assays used by Allergan and Merz, which were both approved for batch release, were not the same and different products were likely to behave differently in different assays. Thus these findings were not contradictory since each company used its own proprietary assay.

Allergan submitted that these observed differences in potency and enzymatic activity supported the non-interchangeability of unit doses of botulinum toxin type A products. The optimum dosage and number of injection sites in the treated muscle should be determined individually for each patient. A titration of the dose should be performed. Physicians should consult the appropriate SPC to obtain product-specific dosage recommendations.

Allergan alleged that the current Merz campaign and claims at issue were misleading and did not reflect the balance of evidence. In particular, significant new data (Moers-Carpi *et al*, 2011) was omitted. These new data from a large (n=220) randomised, double blind, equivalence study directly challenged the hypothesis that the products were interchangeable at a 1:1 dose ratio. The basis for this study was the investigators' experience of the relative clinical effectiveness of the different medicines, the differences seen in the different reference LD50 assays and the different available dose ranging data. Allergan considered that this new data, while not inconsistent with the findings of the Merz non-inferiority studies, clearly challenged the basis for claims of equivalence and a 1:1 conversion ratio.

Allergan alleged that the claims by Merz for 'Equipotency' and '1:1 Conversion' between Xeomin/Bocouture and Vistabel/Botox was a source of significant concern. No 'dosing conversion' occurred or should be implied from the non-inferiority studies conducted by Merz. The direct medical impact was that a significant patient safety risk existed with prescribers encouraged to transfer information from one product to another.

Allergan alleged that the advertisements and Merz's campaign based around these core claims were inaccurate, misleading, could not be substantiated and were not based on an up-to-date evaluation of all the available evidence. Breaches of Clauses 7.2, 7.3 and 7.4 were alleged.

Allergan noted that in Case AUTH/2270/10/09 it was ruled that the results of a non-inferiority study could not be used to claim equivalence. Merz's own submission in that case was that it had no data to support a claim that Xeomin was equivalent to Botox and Allergan believed that this was still so; Merz had not published any new clinical data that supported a claim of equivalence. Therefore, Allergan believed the claims for 'Equipotency' and '1:1 Conversion' between Xeomin/Bocouture and Vistabel/Botox (ie equivalence) were in breach of the undertaking in Case AUTH/2270/10/09 and in breach of Clause 25.

When writing to Merz the Authority asked it to respond to Clauses 2 and 9.1 in addition to the clauses cited by Allergan.

RESPONSE

Merz submitted it was important to clarify the background and inter-company dialogue between the companies.

In January 2012 Allergan complained about two Bocouture leavepieces (refs 1059/BOC/May/2011/JH and 1059/BOC/MAY/2011/JH), a Bocouture advertisement (ref 1070/MER/AUG/2011/JH) and a Xeomin advertisement (ref 1281/XEO/OCT/2011/JL). As a consequence Merz promptly withdrew one of the leavepieces (ref 1059/BOC/MAY2011/JH) and upon review of all other current promotional material identified an advertisement (ref 1075/BOC/DEC/2011/JH) which was exactly the same as the leavepiece and so it too was withdrawn at the same time as a direct consequence of the inter-company dialogue. Merz stated that it had provided copies of both withdrawal certificates.

Merz stated that it had not received a complaint from Allergan about this advertisement either before or after its withdrawal. The fact that the Bocouture advertisement (ref 1075/BOC/DEC/2011/JH) was now the subject of Allergan's complaint with no prior inter-company dialogue represented an unusual circumstance which in Merz's view might not be consistent with the Constitution and Procedure.

Merz noted that in Case AUTH/2270/10/09 Allergan complained about the claim 'At least as effective as Botox with a similar safety profile'. The Panel ruled that it was misleading as it implied 'possible superiority'. Merz consequently undertook not to use the claim and noted that neither it nor any suggestion of superiority of Xeomin/Bocouture over Vistabel/Botox appeared in the advertisements now at issue. Merz did not consider that there was a breach of undertaking and as such Clause 25 could not be applied to the materials at issue.

Merz noted Allergan's submission that Case AUTH/2270/10/09 ruled that non-inferiority studies could not be used to claim 'equivalence'. It should be noted that the material considered in both Case AUTH/2270/10/09 and the current case (Case AUTH/2496/4/12) did not contain a claim of 'equivalence'. This was because equivalence was a specific statistical term used to describe a specific statistical test.

Merz considered that Allergan had sought to leverage the protected status of the word 'equivalence', conferred on it by its specific meaning, and make it all encompassing to cover any term which related to comparability or similarity. This point arose in Case AUTH/2357/9/10 in relation to the promotion of Pradaxa. In that case the Panel ruled that an image of a set of scales accompanied by the claim '…efficacy and safety equivalent to …' was not supported by the non-inferiority studies cited. The Panel also ruled, however, that the claim '… efficacy and safety comparable to…' was substantiated by the non-inferiority studies cited. Upon appeal the Appeal Board further reinforced that 'comparable' did not imply 'equivalence'. Merz did not consider that the terms used in the advertisements were interchangeable with or implied equivalence, which, as established in previous cases, was not a general term but had a very specific meaning.

Merz submitted that the claims at issue were specifically chosen as they were the Medicines and Healthcare products Regulatory Agency's (MHRA's) approved descriptors of relative potency, as expressed in the Bocouture and Xeomin SPCs as outlined below.

Section 4.2 Xeomin 50U SPC:

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

Section 4.2 Bocouture 50U SPC:

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

Merz submitted that the use of the statements 'clinical studies suggest … equipotent' or 'equal potency' were very different to the implication of 'At least as effective as Botox with a similar safety profile'. They did not imply superiority and they were consistent with the MHRA's position. Further to this, while not the subject of the undertaking, none of the advertisements used the term 'equivalent' to describe the outcomes of clinical comparisons. Merz thus denied a breach of Clauses 2 and 25.

Merz submitted that Allergan had falsely stated that the campaign would lead prescribers to conclude that units of potency were interchangeable between brands and that Xeomin/Bocouture and Vistabel/Botox were equivalent. This assertion was undermined by the fact that all of the material at issue stated that units of potency were not interchangeable and none of the materials included a claim of equivalence.

Allergan had sought to confuse the objectives of the PhVWP, to clarify that each particular brand had its own unit of potency, with the ability to compare the clinical efficacy of products when used in patients. Merz considered that the two statements positioned one after the other in the relevant SPCs of Xeomin and Bocouture, and reviewed below, were supplementary in nature, not contradictory. The first sentence in each SPC provided the prescriber with information that related to the assay. As Allergan had previously shown, by using the Allergan assay for Vistabel/Botox and Xeomin/Bocouture an apparent difference in unit doses measured was seen (Hunt *et al*). Because of this both manufacturers used their own specific product assays. The second sentence in each SPC informed prescribers that in the clinical setting, ie that which was most relevant to health professionals, the two products demonstrated similar results (an equal potency of the product appeared to have been demonstrated) when a dosing conversion ratio of 1:1 was used. These statements co-existed on the SPCs because they were both factually correct and were related to different situations. They were not contradictory.

Section 4.2 Xeomin 50U SPC:

> 'Due to differences in the LD50 assay, Xeomin units are specific to Xeomin. Therefore unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.
>
> 'Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [Botox] are of equal potency when used with a dosing conversion ratio of 1:1.'

Section 4.2 Bocouture 50U SPC

> 'Unit doses for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.
>
> Comparative clinical study results suggest that Bocouture and the comparator product [Botox] containing conventional Botulinum toxin type A complex (900 kD) are of equal potency.'

Merz submitted that the advertisements were faithful and unambiguous representations of the respective product SPCs, which were founded on head-to-head matched dose non-inferiority studies using a 1:1 dosing ratio designed with the scientific advice of the European Medicines Agency and accepted by the regulators in 28 countries. They did not imply superiority nor did they state that the product unit doses were equivalent or had been tested for equivalence.

Merz submitted that the statements allowed prescribers to make a considered comparison between products. The quotations in the advertisement were deliberately taken from the SPCs because they were the MHRA endorsed position. The accompanying visual did not mislead as to the comparison, denigrate or distort the relationship between the brands and supported the SPC statements on relative potency. The lasting impression was that clinical studies suggested 1 unit of Vistabel/Botox was comparable to 1 unit of Xeomin/Bocouture.

Merz submitted that the fully referenced advertisements reflected the clinical registration data represented by the SPC. They did not omit published, peer reviewed, controlled, comparative, non-inferiority studies. Whilst the advertisements did not specifically refer to the Allergan sponsored Hunt and Clarke pre-clinical data (the subject of Cases AUTH/2346/8/10 and AUTH/2335/7/10), nor the Allergan sponsored non-controlled Moers-Carpi *et al* (the subject of Cases AUTH/2489/3/12 and AUTH/2487/3/12), Merz did not believe that this made the advertisements based on the product registration data misleading or inaccurate. This was because the Hunt and Clarke data did not address the clinical situation which was paramount and Moers-Carpi *et al* did not directly compare the relative product potencies as the doses were not matched.

Based upon these arguments Merz did not consider that the advertisements were in breach of Clauses 7.2 or 7.3. Additionally the claims could be substantiated and were the unambiguous view of the regulator which, Merz assumed, took in to account the PhVWP (2006) opinion when it granted the product licence. The advertisements therefore were not in breach of Clause 7.4.

Finally, Merz submitted that the advertisements in question were consistent with the standards for the advertising of medicines. They included straightforward images of the products and unambiguously supported the relative potency statements in the product SPCs. As such Merz considered that high standards had been maintained and it thus denied a breach of Clause 9.1.

PANEL RULING

The Panel noted that the advertisements at issue were all different to one another and so in that regard each one was considered separately.

- Bocouture advertisement (ref 1070/MER/AUG/2011/JH)

In that regard, it appeared that inter-company dialogue had been successful and so the Director decided that only the alleged breach of undertaking would be considered.

- Bocouture advertisement (ref 1075/BOC/DEC/2011/JH)

The Director noted Merz's submission that this advertisement had not specifically been the subject of inter-company dialogue. However, the advertisement featured some of the claims at issue and so in that regard the Director considered that it was another example of the material which the two companies had discussed and was thus covered by the inter-company dialogue. The Director further noted Merz's submission that the advertisement had been withdrawn as a result of inter-company dialogue about a leavepiece. However, the evidence of withdrawal provided, dated 20 January 2012, related to the Bocouture advertisement (ref 1070/MER/AUG/2011/JH) above. The Director considered that on the evidence before her the advertisement (ref 1075/BOC/DEC/2011/JH) had not been withdrawn and as it featured claims which had been the subject of inter-company dialogue, the complaint about it could proceed.

The Panel noted that the advertisement featured a photograph of a vial of Bocouture and a vial of Botox side-by-side. Above the vials was the claim in bold, blue font 'In glabellar frown lines, clinical studies suggest Bocouture vs Botox: Equal Potency 1:1 Clinical Conversion Ratio'. This claim and the photograph took up over half of the advertisement. Below the vials was a thick blue horizontal line beneath which was the statement in smaller black font 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'. This statement and the claim for equal potency were referenced to the Bocouture SPC. The claim for a 1:1 clinical conversion ratio was referenced to Sattler *et al* (2010).

The Panel noted that in Section 4.2 of the Bocouture SPC, Posology and method of administration, the first statement in bold type read 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxins'. A similar bold statement also appeared in the Xeomin SPC. The Panel noted the prominence of these statements in the SPCs and considered that although the statement from the Bocouture SPC had been included in the advertisement at issue, it was given significantly less prominence than the other claims. Given its position below the thick blue line, it appeared to be separate from the main part of the advertisement. The prominence given to this statement in the SPC had not been reflected in the advertisement. The Panel considered that the advertisement was misleading in that regard. A breach of Clause 7.2 was ruled.

The Panel noted that the claim '…clinical studies suggest… Equal Potency…' was referenced to the Bocouture SPC. The relevant statement in the SPC stated 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'. The second part of the claim in the advertisement '1:1 Clinical Conversion Ratio', was referenced to Sattler *et al*, a non-inferiority study which had demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin (n=277) to Vistabel/Botox (n=93) in the treatment of glabellar frown lines. The Panel noted that it had previously been established that non-inferiority studies could not be used to imply equivalence.

The Panel considered that the overall impression from the advertisement was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, the advertisement encouraged prescribers to consider that the unit doses of Bocouture and Botox were interchangeable. The Panel considered that the advertisement was misleading in that regard and a breach of Clauses 7.2 and 7.3 was ruled. The Panel considered that the impression given by the advertisement could not be substantiated. A breach of Clause 7.4 was ruled.

- Xeomin advertisement (ref 1281/XEO/OCT/2011/JL)

This advertisement featured a photograph of a vial of Xeomin and a vial of Botox side-by-side with a colon (:) between them. The photograph was surrounded by what appeared to be a line drawing of an ornate picture frame. The headline claim read 'Clinical studies suggest Xeomin and Botox are equipotent, with a conversation ratio of 1:1 Xeomin SPC'. Below the photograph of the vials, ie beneath the 'picture frame', on the left-hand side was the statement 'Always prescribe by brand, unit doses are not interchangeable'. This was referenced to the Xeomin 50U SPC. The headline claim and the statement below the 'picture frame' were in a similar prominent white font on a black background.

The Panel noted that Section 4.2 of the Xeomin 50U SPC stated the following:

> 'Due to unit differences in the LD50 assay, Xeomin units are specific to Xeomin. Therefore unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.
>
> Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1'.

The Panel noted the prominence given to the first statement in the SPC and that the order of the two statements in the SPC had effectively been reversed

in the advertisement, which resulted in the claim 'Clinical studies suggest…' being used as the headline to the advertisement. The Panel considered that the relative emphasis on the two statements in the SPC had not been reflected in the advertisement. In the Panel's view, the advertisement encouraged prescribers to consider the unit doses of Bocouture and Botox were interchangeable. The Panel considered that the advertisement was misleading in this regard. A breach of Clauses 7.2 and 7.3 was ruled. The Panel considered that the impression given by the advertisement could not be substantiated. A breach of Clause 7.4 was ruled.

- Alleged breach of undertaking

The Panel noted its comments above about the Bocouture advertisement (ref 1070/MER/AUG/2011/JH) and inter-company dialogue and the alleged breaches of Clauses 7.2, 7.3 and 7.4. The Panel noted that inter-company dialogue was not required in relation to an alleged breach of undertaking (Clauses 2, 9.1 and 25) and thus considered that that aspect of the complaint would be considered in relation to all three advertisements at issue.

The Panel noted that in Case AUTH/2270/10/09, Merz had been ruled in breach of the Code for claiming that Xeomin was 'At least as effective as Botox with a similar safety profile'. The Panel considered that the claim implied possible superiority of Xeomin vs Botox which was not supported by the available data. A breach of the Code was ruled which was upheld on appeal.

Turning to the case now before it, the Panel noted that the advertisements at issue referred to Xeomin/Bocouture being 'equipotent' or having 'Equal Potency' to Botox/Vistabel. There was no suggestion that Xeomin/Bocouture might be more potent than Botox/Vistabel. In that regard the Panel did not consider that the advertisements were in breach of the undertaking given in Case AUTH/2270/10/09. No breach of Clause 25 was ruled. The Panel subsequently ruled no breach of Clauses 2 and 9.1.

APPEAL BY ALLERGAN

Allergan appealed the Panel's ruling of no breach of Clause 25. As the Panel's rulings of no breach of Clauses 2 and 9.1 (cited by the Authority in this case) were as a direct consequence of its ruling of no breach of Clause 25, Allergan's appeal was also taken as an appeal of those clauses.

Allergan noted that the claims 'Equal Potency' or 'Equipotent' and '1:1 Clinical Conversion ratio' or 'Conversion ratio of 1:1' appeared alongside a visual of either Bocouture/Xeomin or Vistabel/Botox vials standing side-by-side. Allergan alleged that the visual clearly emphasised a direct 1:1 equivalence/conversion of the two medicines. In some of the promotional materials the phrase 'clinical studies suggest' was added. In addition, less prominently and usually in smaller font, was the SPC statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin'.

- Bocouture advertisement (ref 1075/BOC/DEC/2011/JH)

Allergan noted the Panel's ruling that the advertisement was misleading in breach of Clauses 7.2, 7.3 and 7.4. Specifically, 'The Panel considered that the overall impression from the advertisement was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, the advertisement encouraged prescribers to consider that the unit doses of Bocouture and Botox were interchangeable' (emphasis added). The impression given by the advertisement could not be substantiated. The Panel noted that in Case AUTH/2270/10/09 it had been established that non-inferiority studies could not be used to imply equivalence.

- Xeomin advertisement (ref 1281/XEO/OCT/2011/JL)

Allergan noted that the Panel had considered this advertisement misleading in breach of Clauses 7.2, 7.3, and 7.4 in that it encouraged prescribers to consider that unit doses of Bocouture and Botox were interchangeable. The impression given by the advertisement could not be substantiated.

- Breach of undertaking

Allergan noted that, as stated by the Panel and established in Case AUTH/2270/10/09, non-inferiority studies could not be used to claim equivalence. Merz's submission in Case AUTH/2270/10/09 was that it had no data to support a claim that Xeomin/Bocouture was equivalent to Botox/Vistabel and this was still so; Merz had not published any new clinical data to support a claim of equivalence.

In this case the Panel considered that the overall impression from the Bocouture advertisement (1075/BOC/DEC/2011/JH) was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, both advertisements had encouraged prescribers to consider that the unit doses of Xeomin/Botox and Bocouture were interchangeable. The Panel considered that the advertisements were misleading in this regard.

In Allergan's view these misleading claims were caught by the undertaking given in Case AUTH/2270/10/09. Whilst the claim at issue in that case was 'At least as effective as' the Panel's ruling clearly also addressed equivalence.

Allergan noted the following from the Appeal Board's ruling in Case AUTH/2270/10/09: 'The Appeal Board noted Merz's submission at appeal that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's view the claim "At least as effective" not only implied equivalence but also possible superiority which was misleading'.

Therefore, Allergan alleged that any claim which implied clinical equivalence and interchangeability must be in breach of the undertaking given in Case

AUTH/2270/10/09. Allergan therefore appealed the Panel's ruling of no breach of Clause 25.

COMMENTS FROM MERZ

Merz noted that in Case AUTH/2270/10/09 Allergan complained about the use of the claim 'At least as effective as Botox with a similar side effect profile' on an exhibition panel for Xeomin. The Panel ruled that this was misleading as it implied 'possible superiority' of Xeomin vs Botox which was not supported by the available data. The breach was upheld upon appeal and Merz undertook not to use the claim again. The claim or any suggestion of superiority of Xeomin/Bocouture over Botox/Vistabel, did not appear in the advertisements now at issue.

Merz submitted that, as comparative claims between Xeomin and Botox had been the subject of much discussion and dispute, it had taken significant care to ensure that comparisons of the two products were appropriate, could be substantiated, were consistent with the regulator's view and did not breach previous undertakings. Merz was very disappointed that the advertisements now at issue implied that was not intended. However, the advertisements were substantially different from the exhibition panel used in 2009 and at issue in Case AUTH/2270/10/09. As ruled by the Panel, they did not breach the undertaking for Case AUTH/2270/10/09.

Merz submitted that following the Panel's ruling in Case AUTH/2270/10/09 there had been substantial changes to the product lines and available data. Examples of this were that the MHRA approved the 50U Xeomin vial and the licence of Bocouture. Within these documents specific guidance on comparative potency was included in the respective SPCs. Merz considered that the regulatory approved guidance was the most up-to-date perspective on the matter and the language therein the most appropriate way to compare Xeomin with Botox and Bocouture with Vistabel. The SPCs did not refer to superiority and neither did the advertisements.

The claims at issue were:

- Xeomin advertisement (ref 1281/XEO/OCT/2011/JL):

  'Clinical studies suggest Xeomin and Botox are equipotent, with a conversion ratio of 1:1 Xeomin SmPC'.

Section 4.2 of the revised Xeomin 50U SPC stated 'Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [Botox] are of equal potency when used with a dosing conversion ratio of 1:1'.

Merz submitted that the claim used was a contracted but faithful representation of the SPC. The claim was presented as a headline above a visual of the Xeomin and Botox vials and was balanced by the prominent statement below: 'Always prescribe by brand, unit doses are not interchangable' (emphasis added).

Merz noted that the Panel considered that the reversal of the order of the statements taken from the SPC had resulted in the impression that unit doses were interchangeable. Based upon this impression the advertisement was ruled to be in breach of Clauses 7.2, 7.3 and 7.4. There was no indication of an implied superiority in the advertisement or referred to by the Panel ruling.

- Bocouture advertisements (refs 1075/BOC/DEC/2011/JH, 1070/MER/AUG/2011/JH)

  'In glabellar frown lines, clinical studies suggest

  Bocouture vs Botox:
  Equal Potency
  1:1 Clinical Conversion Ratio'.

Section 4.2 of the new Bocouture 50U SPC stated 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [Botox] are of equal potency'.

Merz noted that the statement 'Unit doses recommended for Bocouture are <u>not</u> interchangeable with those for other preparations of botulinum toxin' (emphasis added) was also clearly stated. The Panel concluded that the impression was given that Bocouture had been unequivocally demonstrated clinically equivalent to Vistabel and that prescribers were encouraged to consider the two products' units interchangeable. The advertisements were ruled to be in breach of Clauses 7.2, 7.3 and 7.4. There was no indication of an implied superiority in the advertisements or referred to by the Panel which deemed that they gave the impression of 'equivalent'.

Merz submitted that since the completion of Case AUTH/2270/10/09 in 2010, there had been substantial further data and opinion published which confirmed comparable efficacy for Xeomin/Bocouture and Botox/Vistabel at a 1:1 dose conversion ratio. This was reinforced by a recent meta-analysis of 8 core studies and a further 11 identified studies across a range of indications which concluded 'consequently 50 or 100 units of each product should be considered of equal potency until such time as compelling clinical evidence to the contrary becomes available' (Jandhyala 2012 and Prager *et al*, 2012).

Merz submitted that it had intended to communicate that Xeomin/Bocouture had been demonstrated 'clinically comparable' to Botox/Vistabel which could be substantiated by the growing published data and opinion as well as the respective product SPCs. Indeed, it was fair to question if the claim in Case AUTH/2270/10/09 had been 'As effective as Botox with a similar side effect profile' (rather than 'At least as'), whether it would have been found in breach in the first instance, for implying comparable rather than superior efficacy. The current advertisements did not imply superiority.

In developing the advertisements Merz submitted that it was deliberately cautious and used the language of the SPC (and the registration study) to convey comparable efficacy at a 1:1 clinical conversion ratio reflecting the dosing in the non-inferiority registration trials. Although Merz had not

intended to imply unequivocal equivalence or unit interchangeability which could not be substantiated, with hindsight it accepted the Panel's view on this matter and chose not to appeal. Merz noted that in the Panel ruling it was the 'overall impression' that was given rather than a literal statement of fact; the terms 'equivalent' or 'interchangeable' had not featured in any of the material reviewed in this or Merz's prior cases. If the impression given by the advertisements at issue was that the products were indeed 'interchangeable' and 'equivalent unit for unit' despite saying 'not interchangeable', how could the advertisements have also conveyed a message of superiority, proposing that one product was better than the other?

In summary, Merz supported the Panel's view that the claim 'At least as effective as', which implied superiority, was significantly different from the claims at issue which related to 'equal potency'. The Panel ruled that the advertisements at issue implied that the products were so similar that they were interchangeable, despite clearly stating 'not interchangeable'. If the impression was they were the same/similar, how could they also be found in breach of an undertaking that was based on leaving the impression of superiority?

Merz regretted that despite faithfully using the SPC guidance on potency, the Panel considered that the overall impression was one of unequivocal equivalence and interchangeability. Accepting that misjudgement, Merz submitted that the point at issue was sufficiently different from the prior case not to represent a breach of undertaking. Therefore Merz denied a breach of Clause 25.

Furthermore, Merz submitted that its efforts to stay within the explicit guidance of the product SPCs in developing the advertisements did not represent a failure to maintain high standards nor did it bring discredit upon, or a loss of confidence in, the pharmaceutical industry. Merz thus also denied breaches of Clauses 2 and 9.1.

FINAL COMMENTS FROM ALLERGAN

Allergan agreed with the Panel's rulings that the advertisement at issue were in breach of Clauses 7.2, 7.3 and 7.4. Specifically, 'The Panel considered that the overall impression from the advertisement was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, the advertisement encouraged, prescribers to consider that the unit doses of Bocouture and Botox were interchangeable. …the impression given by the advertisement could not be substantiated.' (emphasis added).

Allergan noted that Merz had not appealed these rulings.

Allergan alleged the claims of 'Equal Potency' or 'Equipotent' and '1:1 Clinical Conversion ratio' or 'Conversion ratio of 1:1' also breached Merz's undertaking given in Case AUTH/2270/10/09.

Allergan noted that the rulings in Case AUTH/2270/10/09 by the Panel and the Appeal Board were not only about an implied claim of 'superiority' as Merz seemed to believe but also in relation to 'comparability' and 'equivalence'. Indeed Merz accepted that there was no evidence to support claims of equivalence. The summary of the case made the ruling very clear:

> 'The Panel considered that there was a difference between showing non-inferiority to showing comparability. The Panel considered on the basis of the data the claim that Xeomin was 'At least as effective as Botox' did not reflect the available evidence. It implied possible superiority of Xeomin as alleged and was misleading. Breaches of the Code were ruled.
>
> Upon appeal by Merz the Appeal Board noted that both parties agreed that Benecke et al and Roggenkamper et al were non-inferiority studies that showed that Xeomin was no worse than Botox by a pre-specified margin (delta) that was clinically acceptable.
>
> The Appeal Board noted Merz's submission that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's view the claim 'At least as effective' not only implied equivalence but also possible superiority which was misleading. The Appeal Board did not consider that the claim could be substantiated by the available data. The Appeal Board upheld the Panel's ruling of breaches of the Code.'

Allergan submitted that as stated by the Panel in this case, and established in Case AUTH/2270/10/09, non-inferiority studies could not be used to claim equivalence and the Panel also noted there was a difference between demonstrating 'non-inferiority' and 'comparability'. Merz had submitted in Case AUTH/2270/10/09 that it had no data to support a claim that Xeomin/Bocouture was equivalent to Botox/Vistabel. This was still so; Merz had not published any new clinical data to support a claim of equivalence.

Allergan submitted that, in its response to the appeal, Merz erroneously referred to the 'new' and 'revised' SPCs for Xeomin and Bocouture when in fact referring to statements in Section 4.2 of its previous SPC, claiming 'equal potency' which had been removed at the regulator's request. (Current Merz Xeomin and Bocouture SPCs effective March 2012).

Allergan noted Merz's claim that it was deliberately cautious and used language to convey comparable efficacy at a 1:1 clinical conversion ratio which in itself was contrary to the Panel ruling in Case AUTH/2270/10/09. Thus Allergan submitted Merz's intent was in breach of the undertaking.

Allergan also noted Merz's reference to substantial further data and opinion confirming comparable efficacy and its reference to a meta-analysis of 8 studies (Jandhyala). Merz also cited, but did not discuss, a retrospective analysis of daily practice in treatment of the upper face (Prager *et al*).

Allergan noted that in Jandhyala mixed treatment comparisons meta-analysis, only 8 clinical studies were identified in the literature search three of which compared Dysport with placebo and were not relevant for inclusion in the analysis. Of the five applicable studies, four compared Botox (20U) with placebo. No Xeomin vs placebo studies were included in the analysis. The fifth study (Sattler *et al*) involved a Xeomin treatment arm but differed significantly from the Botox vs placebo studies included as evidence for the Botox effect size:

a) it was a non-inferiority study and not placebo controlled
b) the investigators were not blinded
c) the dose of Botox (24U) differed from the dose applied in the Botox placebo controlled trials (20U)
d) the endpoint cited was a responder definition of a 1 point change on the facial wrinkle scale in contrast to the change to 'none or mild' used in the four Botox placebo controlled trials.

With only one head-to-head study included and no other studies that included Xeomin to add to the evidence of the head-to-head, there seemed no justification for the claim of substantial further data based on this analysis funded by Merz.

Jandhyala appeared to acknowledge the limited data input in the results section where it was stated that at a dose of 24 units each, there was a 94% likelihood of Xeomin producing a better outcome than Botox. This implied that the only analysis performed was comparing the effect sizes of each product in Sattler *et al*, a non-inferiority study.

Allergan submitted that in this case the Panel considered that the overall impression from the Bocouture advertisement (ref 1075/BOC/DEC/2011/JH) was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so (emphasis added).

In the Panel's view, both advertisements encouraged prescribers to consider that the unit doses of Xeomin/Botox and Bocouture/Vistabel were interchangeable. The Panel considered that the advertisements were misleading in this regard.

Allergan submitted that these misleading claims were covered by the undertaking given in Case AUTH/2270/10/09. Whilst the claim at issue in that case was 'At least as effective as', the ruling clearly also addressed equivalence.

Allergan noted the following section from the Appeal Board's ruling in Case AUTH/2270/10/09.

'The Appeal Board noted Merz's submission at appeal that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's view the claim 'At least as effective as' not only implied equivalence but also possible superiority which was misleading.'

Therefore, Allergan submitted that the claims found in breach which implied clinical equivalence and interchangeability were in breach of the undertaking given in Case AUTH/2270/10/09.

APPEAL BOARD RULING

The Appeal Board noted its ruling in Case AUTH/2270/10/09 stated that:

> 'The Appeal Board noted Merz's submission at the appeal that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's view the claim 'At least as effective as' not only implied equivalence but also possible superiority which was misleading. The Appeal Board did not consider that the claim could be substantiated by the available data. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3.'

The Appeal Board noted that the undertaking in that case related to a claim that not only implied equivalence but also possible superiority; its ruling had been made on both aspects. In the current case, Case AUTH/2496/4/12, Allergan's allegation regarding a breach of undertaking, the subject of the appeal, related only to claims of equivalence.

The Appeal Board noted that to date there was still no data to show whether Xeomin/Bocouture was equivalent to Botox/Vistabel. Now, as when the ruling in Case AUTH/2270/10/09 was made, there were only non-inferiority studies which showed that the medicines were no worse than each other by a clinically acceptable pre-specified margin.

Turning to Case AUTH/2496/4/12, the Appeal Board considered that the Bocouture advertisement (ref 1075/BOC/DEC/2011/JH) which featured the claim 'In glabellar frown lines, clinical studies suggest' followed by 'Bocouture vs Botox:', 'Equal potency' and '1.1 Clinical Conversion Ratio' together with the visual beneath of a vial of each of the medicines side-by-side, implied to prescribers that the two products were clinically equivalent and that unit for unit they were interchangeable. The Appeal Board considered that although the claim at issue was not the same as that in Case AUTH/2270/10/09, it was sufficiently similar with regard to a claim for 'equivalence' for it to be covered by the undertaking previously given. The Appeal Board thus ruled a breach of Clause 25. The appeal on this point was successful.

Similarly the Appeal Board considered that the Xeomin advertisement (ref 1281/XEO/OCT/2011/JL) which featured the claim 'Clinical studies suggest Xeomin and Botox are equipotent, with a conversion ratio of 1:1 Xeomin SmPC' together with a visual beneath of a vial of each medicine side-by-side with a colon between them, again implied to prescribers that the medicines were clinically equivalent and that unit for unit they were interchangeable. The Appeal Board noted its comments above and thus ruled a breach of Clause 25. The appeal on this point was successful.

The Appeal Board noted that the Bocouture advertisement included the statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin' and the Xeomin advertisement similarly included the statement 'Always prescribe by brand, unit doses are not interchangeable'. These statements were referenced to the respective products' SPCs and in both advertisements they appeared in a less prominent position and smaller font than the claims and visuals that implied clinical equivalence. The Appeal Board considered that implying that the products were clinically equivalent and hence interchangeable was contrary to statements in the SPCs. The Appeal Board considered that this raised possible patient safety concerns.

The Appeal Board considered that as Merz had no data on which to base the implied claims of clinical equivalence, and as it had breached its undertaking and assurance in Case AUTH/2270/10/09, it had failed to maintain high standards and it had thus brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled breaches of Clauses 9.1 and 2. The appeal on this point was successful.

Complaint received **5 April 2012**

Case completed **9 August 2012**

ALK-ABELLÓ v MEDA

Promotion of EpiPen

ALK-Abelló complained about a booklet entitled 'The Case for Epipen (Adrenaline) Auto-Injector'. The booklet was sent by Meda Pharmaceuticals to pharmacy leads working at senior levels within primary care organisations (PCOs) as a response to several PCOs recommending a switch to Jext adrenaline auto injector from EpiPen. Both EpiPen and Jext were adrenaline auto injectors for treatment of allergic emergencies.

ALK-Abelló alleged that, with regard to Section 7 entitled 'The risks of changing from EpiPen Auto-Injector', Meda deliberately implied that there were life-threatening risks caused by changing from EpiPen to another adrenaline auto injector. Readers were likely to infer that the risk was associated with Jext as the majority of the booklet compared EpiPen to Jext. Meda was unable to substantiate the heading which was alleged to be misleading, not capable of substantiation and disparaging.

The detailed response from Meda is given below.

The Panel considered that it was not unreasonable to assume that there were risks involved in switching a patient's treatment from one on which they were already established and with which they were familiar. The risks would vary depending on the differences in treatment and the nature of the condition being treated. It noted that anaphylactic shock was a rare event but could have serious consequences.

The Panel considered that the reference to the implications for patients of not knowing how to use their auto injector in an emergency being 'life-threatening' would apply to all devices. There was no implication that the decision to switch from EpiPen was 'life-threatening', nor was any other specific auto injector mentioned in that regard. In the Panel's view it was not unreasonable to stress the need to ensure that appropriate training was given when anaphylactic patients were changed to a different auto injector.

The Panel did not consider that the reader would infer that the risks in Section 7 were associated with Jext as, in ALK-Abelló's view, the majority of the booklet compared EpiPen to Jext. This was not so. Sections 1-7 either discussed auto injectors in very general terms or identified all three available auto injectors without attaching disproportionate weight to any one, including Jext.

Overall, the Panel considered that there was no implication that switching patients to Jext put them at risk as alleged. On this narrow point the section was not misleading and nor was Jext disparaged. The Panel ruled no breach of the Code.

ALK-Abelló Limited complained about a booklet entitled 'The Case for Epipen (Adrenaline) Auto-Injector' (ref UK/EPI/11/0053d). The booklet was sent by Meda Pharmaceuticals to pharmacy leads working at senior levels within primary care organisations (PCOs) as a response to several PCOs recommending a switch to Jext adrenaline auto injector from EpiPen.

Meda marketed EpiPen and ALK-Abelló marketed Jext. Both products were adrenaline auto injectors for treatment of allergic emergencies.

Meda stated that it was grateful to ALK-Abelló for highlighting aspects where the booklet at issue could be improved, however the overall booklet was not unbalanced.

The booklet was mailed to pharmacy leads in primary care trusts (PCTs). Meda stated that it was clear that the booklet was not intended to be a simple two-page 'flyer', but a comprehensive document that presented a meaningful comparison between alternative adrenaline auto injectors. The primary objective was to draw attention to the differences between the products so that purchasing leads had relevant information on which to make purchasing decisions.

Products like EpiPen, Anapen and Jext were used when a patient experienced an anaphylactic reaction. In such emergency situations the patient might have only minutes to correctly administer treatment before their reaction to the allergen became life threatening. EpiPen had been the standard treatment for over 15 years, whereas Anapen and Jext had more recently entered the market.

Meda submitted that previous issues raised with the Authority related to the difference in administration technique between Jext and EpiPen, for example Cases AUTH/2405/5/11 and AUTH/2462/12/11. While the Panel did not uphold Meda's complaints that ALK-Abelló had failed to completely explain the administration technique for Jext, Meda strongly believed that the differences in administration technique between the two products were an important consideration for patients. At no point had Meda indicated that any product was better or worse than another with respect to efficacy or safety and had focused the comparison on the need to ensure that patients were taught the new administration technique, which Meda considered was the responsible position to take.

Meda understood that competitors and customers might take a different position regarding the need or otherwise for patient training in a new product, however, it considered it was important for those making purchasing decisions, who might be otherwise of the belief that the products were fully

interchangeable, had appropriate information to make an informed decision.

The booklet at issue contained seven main sections, in addition to a summary, prescribing information and references. Section 2 gave a brief overview of anaphylaxis and listed all three products without making any attempt to differentiate in any way. Section 3 highlighted the national guidelines. Section 4 highlighted the need for training in device use. Section 5 highlighted the support package provided by Meda specifically for EpiPen auto injector while section 6 highlighted the management considerations that needed to be made when switching in products is envisaged.

1 'The risks of changing from EpiPen Auto-Injector'.

This statement was the title for Section 7 of the booklet.

COMPLAINT

ALK-Abelló alleged that Meda deliberately implied that there were life-threatening risks caused by changing from EpiPen to another adrenaline auto injector. The reader was likely to infer that the risk was associated with Jext as the majority of the document compared EpiPen to Jext. Meda had previously made similar unfounded allegations about Jext to the PMCPA in Case AUTH/2462/12/11. Meda was unable to substantiate the allegations in Case AUTH/2462/12/11 and in inter-company dialogue for the case now at issue was again unable to substantiate the allegation in the booklet at issue, claiming that 'headings' could not be misleading and did not require substantiation.

ALK-Abelló alleged that this section was in breach of Clauses 7.2, 7.4 and 8.1.

RESPONSE

Meda submitted there was a significant difference between an 'exaggeration' and claiming a product caused 'life threatening risks'. There was also a difference between identifying a risk and claiming that risk was life threatening when considering the allegation with respect to Clause 8.1.

Meda submitted that, contrary to ALK-Abelló's comment, Meda did recognise that headings could be regarded as claims and that headings indicated the context of the following text. During the inter-company dialogue Meda noted that this heading was not a claim per se, but a statement indicating the content of the following paragraphs.

Meda noted ALK-Abelló's allegation that in this section Meda deliberately implied that there were 'life threatening risks' caused by changing from EpiPen to another adrenaline auto injector and that a reader was likely to infer that the risk was associated with Jext, as the majority of the document compared EpiPen to Jext.

Meda did not consider that the allegations were specific and did not correlate with the content of the section. There was nothing in Section 7 (or any part of the document) that indicated any comment on the safety of Jext. In fact the word Jext did not appear in the section at all. The full text was:

'Patients with anaphylaxis ensure that they avoid the allergy triggers and as such anaphylactic shock is a rare event for most patients. Patients need to be prepared, ensuring that they carry two adrenaline auto injector pens at all times and making sure that they and their relatives/carers know how to administer it in an emergency.

Moving anaphylactic patients away from the auto injector device with which they are familiar needs to be well planned; ensuring adequate training is in place for patients and the many groups that need to be able to use an adrenaline auto injector in an emergency.

Using an auto injector correctly is vitally important and any strategy of a PCT to move away from EpiPen Auto-Injector should not underestimate the size of the task to be undertaken in training individuals in adrenaline auto injector use. Indeed the implications for patients of not knowing how to use their adrenaline auto injector in an emergency are life threatening.'

Meda submitted that it failed to see how the need to ensure patients were trained in correct injection technique was in any way disparaging or misleading. It would be irresponsible not to train on administration technique.

Since it did not make the alleged claim (that there were 'life threatening risks' caused by changing from EpiPen to another adrenaline auto injector), Meda denied any breach of Clause 7.2. It could not therefore be in breach for not substantiating a claim that it did not make. Meda also denied that the section disparaged Jext; the booklet did not indicate Jext needed additional training or that it was inferior to EpiPen auto injector, only that all auto injectors required training in administration technique. Meda therefore denied any breach of Clause 8.1.

PANEL RULING

The Panel noted that Section 7 'The risk of changing from EpiPen Auto-Injector' discussed patient preparedness and training in relation to anaphylactic shock generally and included one sentence about the need for training if a patient was moved from a device with which they were familiar. The final paragraph noted the importance of using the auto injector correctly and advised that PCTs moving away from EpiPen should not underestimate the size of the training task. The final sentence read 'Indeed the implications for patients of not knowing how to use their auto-injector in an emergency are life-threatening'.

The Panel considered that it was not unreasonable to assume that there were risks involved in switching a patient's treatment from one on which they were already established and with which they were familiar. The risks would vary depending on the differences in treatment and the nature of the condition being treated. It noted that anaphylactic shock was a rare event but could have serious consequences.

The Panel considered that the reference to the implications for patients of not knowing how to use their auto injector in an emergency being 'life-threatening' would apply to all devices. There was no implication that the decision to switch from EpiPen was 'life-threatening', nor was any other specific auto injector mentioned in that regard. In the Panel's view it was not unreasonable to stress the need to ensure that appropriate training was given when anaphylactic patients were changed to a different auto injector.

The Panel did not consider that the reader would infer that the risks in Section 7 were associated with Jext as, in ALK-Abelló's view, the majority of the booklet compared EpiPen to Jext. This was not so. Sections 1-7 either discussed auto injectors in very general terms or identified all three available auto injectors without attaching disproportionate weight to any one, including Jext. The Panel noted that whilst the subsequent double page spread at Sections 8.1 and 8.2 compared EpiPen and Jext it did not consider that the reader would view the preceding section (Section 7.2) in light of such subsequent comparisons. Overall, the Panel considered that there was no implication that switching patients to Jext put them at risk as alleged. On this narrow point the section was not misleading and nor was Jext disparaged. The Panel ruled no breach of Clauses 7.2 and 8.1. As no claim was made in relation to Jext the Panel thus ruled no breach of Clause 7.4.

Complaint received **27 April 2012**

Case completed **4 July 2012**

ANONYMOUS EX-EMPLOYEE v SANOFI

Activities of sales and medical teams

An anonymous complainant who stated he/she was an ex-employee of Sanofi, alleged that members of the medical oncology team were being pressurised to proactively generate contacts with key oncologists and contact rates were regularly monitored to reinforce the point. The complainant considered that the medical team was, at times, asked to act as an extra sales team. The complainant understood the role to be a reactive one to customer requests, however, he/she was pushed to promote unlicensed medicines. The complainant also alleged that sales representatives were instructed to make more calls per year than allowed under the Code and to ask health professionals for support in challenging a decision by the National Institute for Health and Clinical Excellence (NICE).

The detailed response from Sanofi is given below.

The Panel noted that the complainant was anonymous and non-contactable and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and, like all complaints, judged on the evidence provided by the parties.

The Panel noted that one of the key results/accountabilities for the scientific advisors was to proactively 'engage with external stakeholders in the exchange of "within licence" scientific data in a balanced, non-promotional manner and not in conjunction with any promotional-related person or activity'. The Panel considered that, given the definition of promotion in the Code, the proactive element of the role was promotional and so the scientific advisors had a mixed role – non-promotional and promotional. When carrying out their promotional role, the scientific advisors were thus covered by the specific requirements in the Code for representatives (as defined in the Code).

The Panel noted that the complainant had provided no evidence in relation to the allegations on contact rates. Sanofi broadly expected scientific advisors to achieve a certain number of customer contacts per week to include face-to-face contacts, meetings, substantive email response or telephone calls. The Panel considered that there was no evidence to suggest that a call rate had been set that exceeded the restriction in the supplementary information to the Code and ruled no breach. The Panel was concerned that Sanofi had not provided any relevant briefing document regarding the expected contacts per week but considered that there was no evidence before it to suggest that the scientific advisors were briefed in a way that would advocate, directly or indirectly, a course of action which would be likely to lead to a breach of the Code and no breach was ruled.

The Panel considered that there was no evidence before it to suggest that the scientific advisors had proactively informed health professionals about medicines that did not have a marketing authorization and no breach of the Code was ruled.

With regard to the allegation that Sanofi representatives had asked health professionals for support in challenging a decision by NICE the Panel noted Sanofi's submission that the representative in question had contacted a health professional to request support for a Cancer Drugs Fund (CDF) application for Jevtana (cabazitaxel) funding within one region. The Panel was concerned that there was no written briefing instructions on the process but considered that there was no evidence before it to suggest that the representative in question or Sanofi had failed to maintain high standards in relation to this contact. No breaches of the Code were ruled.

The Panel noted its rulings above and consequently ruled no breach of Clause 2.

An anonymous, non-contactable complainant who stated he/she was an ex-employee of Sanofi, alleged that members of the medical oncology team were being pressurised to proactively generate contacts with key oncologists and were required to adhere to contact rates against which they were regularly monitored. In addition, the complainant alleged that sales representatives were instructed to make a number of calls per year which exceeded that stipulated in the Code and they contacted health professionals to gain support in challenging a decision by the National Institute for Health and Clinical Excellence (NICE).

When contacting Sanofi the Authority asked it to respond in relation to the requirements of Clauses 3.1, 15.2, 15.4, 15.9, 9.1 and 2.

COMPLAINT

The complainant alleged that during his/her time in the medical team he/she was constantly pressurised to proactively generate contacts with key oncologists and contact rate tables were presented against which the team was regularly monitored to reinforce the point.

The complainant stated that it was only recently that the medical team was excluded from sales team and sales strategy meetings. Previously the medical team discussed key customers and sales, and at times the complainant considered that the medical team had been asked to act as an extra sales team.

The complainant alleged that the target number of customers he/she had been given to see over a specific period of time could only be met if the team worked proactively. The complainant always

understood the role to be a reactive one to customer requests. However, he/she was pushed to carry out this promotion for a group of unlicensed medicines such as the parp inhibitor, cabazitaxel, ombrabrulin, larotaxel and alvocidib.

The complainant further alleged that the sales team was consistently instructed to plan at least 12 calls a year on key customers and it was only following the recent integration with Genzyme, whose sales team refused to carry out this mandate; they strongly stated that if they were forced to do more than what the Code stipulated they would complain. In the last few weeks communication was sent out to ignore and change the 12 contact rule.

The complainant alleged that a greater transgression occurred when cabazitaxel (Jevtana) was denied NICE approval last year. The sales team was instructed to proactively ask key customers to write to NICE to challenge the decision and show support. One of the complainant's colleagues had referred to an email from a representative who had followed the above strategy and then received an email from a consultant oncologist who stated that he believed the representative's request to be unethical and unprofessional.

The complainant stated that if a proper investigation was carried out more transgressions would be found. However, due to fear of the current regime and retaliation, currently employed individuals would not openly volunteer this information. The complainant had to leave to even have the courage to highlight certain issues around Sanofi Oncology regularly operating outside of the Code.

RESPONSE

Sanofi submitted that it had a clear, well communicated and confidential whistle-blower policy which allowed any employee to make representation if they were concerned about any activity within the company. In addition, the Sanofi Oncology scientific advisor team (of which the complainant claimed to be a former member) enjoyed a very open management style and had meetings every six to eight weeks at which any topic could be freely and openly discussed. None of the issues raised in the complaint had ever been brought to Sanofi's attention via either of these routes.

Sanofi submitted that its oncology scientific advisors were responsible for providing customers with balanced, non-promotional scientific and technical information. A copy of the scientific advisor job description was provided together with a slide set from a recent training session delivered by the head of promotional affairs and associate medical director, clarifying the role.

Sanofi stated that interviews with the oncology medical manager (to whom the scientific advisor team reported) and a member of the oncology scientific advisor team confirmed that in line with the nature of the scientific advisor role, there were no contact rate targets and contact rates formed no part of the objectives or remuneration target for scientific advisors. Similarly there was no pressure on contact rates. There was a broad expectation of a certain number of customer contacts per week (details were provided) and scientific advisors were also expected to spend one day a week on research or study to maintain their role. There was no requirement for proactive promotion.

Sanofi submitted that with regard to the products mentioned, Jevtana was a licensed product; iniparib, presumably the 'parp inhibitor' [*sic*], was an early stage development candidate; ombrabulin was in late stage development; larotaxel and alvocidib were discontinued from development in February 2010 and November 2010, respectively.

Sanofi stated that Jevtana was comprehensively briefed to the scientific advisors with regard to the mode of action, clinical data and therapeutic area (slides were provided). Iniparib and ombrabulin were mentioned in summary briefs to the scientific advisors so they were aware of the Sanofi oncology pipeline when this information became publicly available (slides were provided).

Sanofi submitted that it had found no evidence of the '12 contact rule' referred to by the complainant and that such a contact rate would be inappropriate and non-compliant.

Sanofi further submitted that it had investigated the topic of scientific advisors being at the same meetings as sales teams. The terms 'sales team and sales strategy' were not used at Sanofi and hence could not be commented upon. Sanofi stated that scientific advisors were at the same sessions as sales teams only when appropriate, eg product or therapeutic area training, general company briefing or training on adverse event reporting, the Medicines Act or the Code. Scientific advisors were not present when promotional activities were discussed or briefed.

Sanofi noted the complainant stated that the sales team was proactively asked to solicit support for the Jevtana NICE review. The sales teams were appropriately briefed on the NICE process for Jevtana with the relevant information provided to health professionals to allow them to make representations to NICE should they wish. Sanofi's investigation had identified no evidence of inappropriate approaches in this respect.

Sanofi stated that the email referred to by the complainant concerned not the NICE review but a request to support the Cancer Drugs Fund (CDF) application for Jevtana funding within one region. The representative in question provided a copy of the email in which a health professional stated, *inter alia*, that the request 'might have put his objectivity & ethical approach at risk', especially as Sanofi had supported his attendance at a European oncology congress. The representative in question had not known that the health professional had been invited to attend the congress; if he/she had, he/she would not have approached him. Subsequent discussion had resolved any misunderstanding with the health professional concerned. A copy of the email was provided.

Sanofi submitted that it had found no evidence to support the complainant's allegations and it thus denied any breach of the Code.

Following a request for further information, Sanofi confirmed that the expected number of clinician contacts per week (face-to-face, at a meeting, through substantive email response or telephone call) was in place prior to the Genzyme integration and had always been an expectation for oncology scientific advisors.

Sanofi stated that the presentation given to clarify the role of the scientific advisors was made to all scientific advisors (oncology, diabetes and cardiovascular/renal) on 20 February 2012. The presentation was not for a specific reason, it was an update/refresher to reinforce the principles that the company followed. There were several new scientific advisors in the post and it was an appropriate topic at the first cross-division medical and scientific affairs meeting of the year in order to confirm current standards and share best practice between new and experienced scientific advisors. Sanofi provided details of the number of the number of oncology scientific advisors in the UK and Ireland and stated that the team reported to the medical manager, oncology (an organogram was provided).

Sanofi submitted that the slides on pipeline products were provided to the oncology scientific advisors to update them when the information became publicly available (these slides were routinely updated on the public Sanofi.com website). No briefing was given as scientific advisors knew that before the content of these slides could be used in communications to customers they would need to be formally reviewed and approved.

Sanofi stated that scientific advisors and commercial colleagues did not meet to discuss key customers and sales or promotional activities or when promotional activities were briefed. As stated above they were only together in relevant sessions such as product or therapeutic area training etc.

Sanofi explained that the scientific advisors' objectives were as described in the job description provided and their bonus was not related to sales performance other then as a factor in overall company performance.

Sanofi confirmed that it had provided the Authority with all material used by the scientific advisors relating to the products mentioned above. There was no written instruction or brief to the sales teams about the NICE approval of Jevtana and soliciting support, nor was there any such written instruction or briefing about contacting health professionals to request support for the CDF application for Jevtana. Sanofi submitted that it concluded that there was no evidence of inappropriate approaches in relation to representatives soliciting support for the Jevtana NICE review following its interview of the sales manager and the representative in question.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and, like all complaints, judged on the evidence provided by the parties.

The Panel noted from the scientific advisor job description that one of the key results/accountabilities for the role was to proactively 'engage with external stakeholders in the exchange of "within licence" scientific data in a balanced, non-promotional manner and not in conjunction with any promotional-related person or activity'. The organogram showed that, through their manager, the scientific advisors had a solid reporting line to a business unit director in addition to a dotted reporting line to the medical director. The slide set which clarified the scientific advisors' role stated that it was non-promotional because the approach was predominantly reactive. The Panel considered, however, that, given the definition of promotion in Clause 1.2 of the Code, the proactive element of the role was promotional which meant that the scientific advisors had a mixed role – non-promotional and promotional. When carrying out their promotional role, the scientific advisors were thus covered by the specific requirements in the Code for representatives (as defined in Clause 1.6), including, *inter alia*, Clauses 15 and 16.

The Panel noted that the complainant alleged that the scientific advisors were constantly pressurised to proactively generate contacts with key oncologists and contact rate tables were regularly presented against which the team were monitored. The Panel further noted the complainant's allegation that the sales team were consistently instructed to plan at least 12 calls per year on key customers.

The supplementary information to Clause 15.4 stated that the number of calls made on a doctor or other prescriber by a representative each year should not normally exceed three on average. This did not include the attendance at group meetings, a visit requested by a doctor or other prescriber, a call made in order to respond to a specific enquiry or a visit to follow up a report of an adverse reaction.

The Panel noted that the complainant had provided no evidence in relation to the allegations on contact rates. Sanofi had submitted that it had found no evidence of the '12 contact rule' but that it had a broad expectation that scientific advisors would achieve a certain number of customer contacts per week to include face-to-face contacts, meetings, substantive email response or telephone calls. The Panel considered that there was no evidence to suggest that a call rate had been set that exceeded the restriction in the supplementary information to Clause 15.4 and ruled no breach of that clause. The Panel was concerned that despite asking it to do so, Sanofi had not provided any briefing document regarding the expected number of customer contacts that the scientific advisors would have per week. However, it considered that there was no evidence before it to suggest that the scientific advisors were briefed in a way that would advocate, either directly or indirectly, a course of action which would be likely to lead to a breach of the Code and no breach of Clause 15.9 was ruled.

The Panel noted the complainant's allegation that he/she, as a scientific advisor was pushed to promote a number unlicensed medicines. Sanofi submitted that iniparib and ombrabulin were mentioned in summary briefs to the scientific advisors so they were aware of the Sanofi oncology pipeline when this information became publicly available. This briefing took place when the information was placed on the Sanofi.com website. The Panel was concerned that there was no briefing to the scientific advisors which clearly stated that they could not proactively share the pipeline information with health professionals; there was no statement on the slides that the information was for in-house use only. However, the Panel considered that there was no evidence before it to suggest that the scientific advisors had proactively provided information to health professionals about medicines that did not have a marketing authorization and no breach of Clause 3.1 was ruled.

The Panel noted the complainant's allegation that Sanofi representatives had contacted health professionals to gain their support in challenging a decision by NICE. Sanofi submitted that the representative in question had in fact contacted a health professional to request support for the CDF application for Jevtana funding within one region. The Panel considered that it was not necessarily unacceptable for companies to ask health professionals to challenge decisions by bodies such as NICE and the CDF, but it must be done in a way that complied with the Code.

The Panel noted from the email response in question that the health professional who had been asked to support the CDF application for Jevtana funding considered that the representative's request 'might have put his objectivity & ethical approach at risk', especially as Sanofi had supported his attendance at a European oncology congress. The Panel further noted Sanofi's submission that the representative in question was unaware that the health professional had been invited by Sanofi to attend the congress and that if he/she had he/she would not have approached him. Subsequent discussion had resolved any misunderstanding with the health professional concerned. The Panel was concerned that there was no written briefing instructions on the process for contacting health professionals to request support for the CDF application. However, the Panel considered that there was no evidence before it to suggest that the representative in question or Sanofi had failed to maintain high standards in relation to this contact. No breach of Clauses 15.2 and 9.1 were ruled.

The Panel noted its rulings above and consequently ruled no breach of Clause 2.

During the consideration of this case, the Panel was concerned to note that Sanofi had provided little in the way of formal briefing documents for the scientific advisors. This was unacceptable and represented poor practice. Given the dual nature of the scientific advisors' role, Sanofi was vulnerable under the Code and had been unable to respond robustly to the allegations made. The Panel noted that the Authority had recently issued informal guidance on Clause 3 of the Code and that this discussed in detail, *inter alia*, the role of medical and scientific liaison executives and the like. The Panel considered that Sanofi would be well advised to review the role of its scientific advisors in the light of that guidance.

Complaint received **9 May 2012**

Case completed **11 July 2012**

CASES AUTH/2506/5/12 and AUTH/2507/5/12

ASTRAZENECA v LILLY and DAIICHI-SANKYO

Efient Leavepiece

AstraZeneca complained about an Efient (prasugrel) leavepiece issued by Lilly and Daiichi-Sankyo.

Efient, co-administered with acetylsalicylic acid (ASA), was indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) or ST segment elevation myocardial infarction (STEMI) undergoing primary or delayed percutaneous coronary intervention (PCI). Section 4.2 of the Efient summary of product characteristics (SPC), Posology and method of administration, stated that in patients with ACS who were managed with PCI, 'premature discontinuation of any antiplatelet agent, including Efient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless discontinuation of Efient is clinically indicated'.

AstraZeneca stated that the leavepiece focussed on the STEMI subgroup of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thromobosis in Myocardial Infarction) study (pivotal registration study for Efient).

TRITON-TIMI 38 (Wiviott *et al*, 2001) was a Phase 3 trial involving patients with moderate to high risk ACS with scheduled PCI and compared Efient with clopidogrel. All patients received ASA. The primary efficacy endpoint was death from cardiovascular causes, non fatal myocardial infarction (MI) or non fatal stroke. The key safety endpoint was major bleeding.

AstraZeneca alleged that the leavepiece was inaccurate, misleading, played down major bleeding/safety considerations, promoted the off-label use of Efient beyond its maximum licensed duration of treatment, and as a result brought the industry into disrepute.

The detailed comments from Lilly and Daiichi-Sankyo are given below.

Page 1 of the leavepiece had across its top, 'Efient Proven Protection for ACS-PCI Patients Receiving Aspirin – Recommended for up to 12 Months'. Beneath, a prominent green band with larger white type bore the claim 'How can you make a difference for your ACS-PCI Patients?' followed by two sub headings 'STEMI Patients' and 'Help Give Your High Risk ACS-PCI Patients Superior Protection Against CV [cardiovascular] Events By Choosing Efient vs Clopidogrel'.

A graph headed 'TRITON-TMI [*sic*] 38, pre-specified STEMI subgroup analysis of the primary efficacy endpoint* and key safety endpoint at 15 months (n=3,534)' was referenced as adapted from Montalescot *et al* (2009). The explanation for * in the graph title was given towards the bottom of page 1 as 'Efient significantly reduced the composite endpoint of CV death, non-fatal MI or non-fatal stroke vs. clopidogrel' and ** as 'No significant difference in incidence of non-CABG [coronary artery bypass graft surgery] related TIMI major bleedings vs. clopidogrel'.**

The graph compared patients treated with clopidogrel + ASA and Efient + ASA in relation to CV death, MI, stroke and days from randomization. Non-CABG TIMI major bleeds were also compared for the two groups. The graph included data from 0 – 450 days from randomization and a vertical dotted line labelled 'Recommended length of treatment' indicated what appeared to be 365 days. On the right hand side of the graph was a prominent downward arrow labelled '21% RRR' [relative risk reduction]. Beneath this the actual risk reduction (ARR) was given in much smaller type 'ARR = 2.4%' p=0.0221' in favour of Efient in relation to CV death, MI, stroke. The comparison of non-CABG TIMI major bleeds did not show a statistically significant difference (p=0.6451).

AstraZeneca alleged that the title of the graph referred to analysis of the primary efficacy endpoint and key safety endpoint at 15 months yet the Efient SPC stated that it was recommended for use in adult patients up to 12 months only. This therefore promoted Efient beyond the terms of its licence and was misleading.

Further the graph illustrated a subgroup analysis of the primary endpoint, including RRR and ARR figures based on outcomes at 15 months. A faint dotted line was presented at 12 months showing the recommended (and therefore licensed) maximum duration of treatment, however the graph continued far beyond this point. The off-licence promotion was compounded by there being no presentation of the actual data, for example ARR and RRR figures, at 12 months. This created the impression that Efient could and should be used in excess of the maximum licensed duration of treatment.

AstraZeneca also alleged that the information was presented as showing no significant difference between Efient and clopidogrel in relation to non-CABG-TIMI major bleeds. While this might be the case in this specific subgroup, in the overall TRITON-TIMI 38 study Efient demonstrated significantly higher rates of non-CABG TIMI major bleeding (2.4% vs 1.8%, p=0.03), life threatening bleeding (1.4% vs 0.9%, p=0.01) and fatal bleeding (0.4% vs 0.1%, p=0.002). There was no mention of the overall results to provide context for clinicians to make an informed decision in relation to these serious

outcomes. AstraZeneca alleged that this was therefore inaccurate, misleading and did not reflect high standards.

The Panel noted that Section 4.2 of the Efient SPC, Posology and method of administration, stated that 'A treatment of up to 12 months is recommended, unless the discontinuation of Efient is clinically indicated …'. The graph at issue on page one of the leavepiece included a dotted line labelled 'Recommended length of treatment' at what appeared to be 365 days from randomization. The calculations for RRR and ARR appeared to be at the end of the study, ie 15 months.

The Panel noted that Section 4.8 (Undesirable effects) and 5.1 (Pharmacodynamic properties) of the Efient SPC referred to data at 14.5 months.

The Panel noted that the 15 month data was taken from the TRITON-TIMI 38 study, a pivitol registration study for Efient. Study visits were conducted at hospital discharge, at 30 days, 90 days and 3 months intervals thereafter for a total of 6 to 15 months. The prespecified subgroup analysis on patients with STEMI included detailed results for major efficacy and safety endpoints at 30 days and 15 months. The primary endpoint was CV death, non-fatal myocardial infarction or non-fatal stroke. The subgroup analysis had not been carried out at 12 months.

The Panel considered that the 15 month data would be of interest to prescribers. The SPC clearly referred to data beyond 12 months. The Panel considered that whilst it was acceptable to refer to the SPC data such references should be secondary to the statement at Section 4.2 of the SPC that treatment of up to 12 months was recommended.

The Panel noted that although the dotted line on the graph did not state the actual length of treatment, it could be approximately determined from the x axis. Neither the dotted line on the graph, nor the strapline at the top of the page which included the phrase 'Recommended for 12 months' were visually prominent. The Panel did not consider that the material on the page in question could be qualified by references to 12 month data in subsequent pages or in the prescribing information. The heading referred to a pre-specified STEMI subgroup analysis of the primary efficacy endpoint and key safety endpoint at 15 months appeared in a highlighted green box and was visually prominent. It made no mention of the recommended duration of treatment. The graph beneath depicted and analysed data at 450 days. The Panel considered that the heading was misleading about the recommended treatment period and consequently inconsistent with the SPC. Breaches of the Code were ruled.

The Panel noted that the graph made claims in relation to primary efficacy outcomes at 15 months. Other than the lines on the graph there was no mention or presentation of the actual ARR, or any other data, at 12 months.

The Panel noted that whilst a dotted line on the graph represented the recommended treatment period by presenting the efficacy and safety results at 15 months prominently with no data at 12 months the graph in effect promoted Efient for 15 months treatment. The 15 month data was not secondary to and or placed within the context of the 12 month recommended treatment period. This was misleading and inconsistent with the SPC recommendation. Breaches of the Code were ruled.

In relation to the results for non-CABG TIMI major bleeds the Panel noted that the subgroup analysis showed no significant difference between clopidogrel + ASA and Efient + ASA. The overall outcome in this regard in TRITON-TIMI 38 was statistically significant in favour of clopidogrel + ASA for the key safety endpoint. Further, the data for life threatening bleeding and fatal bleeding were also in favour of clopidogrel + ASA.

The Panel considered that the allegation that the graph demonstrated a subgroup analysis of non-CAGB TIMI major bleeds at 15 months contrary to the maximum licensed duration of treatment of 12 months was covered by its ruling of a breach set out above.

The overall safety results had not been included and the Panel considered that the subgroup analyses had not been placed in context. The balance of the evidence had not been presented. Breaches were ruled. As the data related to safety endpoints high standards had not been maintained and a further breach was ruled.

Page 2 of the leavepiece was headed 'Make A Difference Now to Protect Their Future'. A bar chart followed by a graph were presented on this page. The main heading to the bar chart was 'Confidence To Reduce The Risk Of Stent Thrombosis vs. Clopidogrel'. The bar chart was headed 'TRITON-TIMI 38: pre-specified STEMI subgroup analysis of the secondary efficacy endpoint of stent thrombosis at 15 months (n=3,534)'. The bar chart was adapted from Montalescot *et al* and compared the incidence of definite or probable stent thrombosis of Efient + ASA and clopidogrel + ASA. A prominent downward arrow labelled '42% RRR' appeared above the Efient bar. The ARR of 1.2%, p=0.0232 was given in less prominent smaller font on the left hand side of the bar chart. The claim 'Efient significantly reduced the risk of stent thrombosis compared with clopidogrel' appeared alongside the heading on the left hand side of the bar chart.

The second half of the page was headed 'Confidence to Reduce Recurrent Cardiovascular Events vs. Clopidogrel' beneath which was the heading 'TRITON-TIMI 38: Landmark analysis of time from first event to second event by randomised therapy (n=1,203)'. The graph below showed data adapted from Murphy *et al* (2008) which compared primary endpoint events (CV death, non-fatal MI or non-fatal stroke) for Efient + ASA and clopidogrel + ASA for 450 days from first event to second event or last follow-up. A dotted line was given on the graph to show recommended length of treatment. The results at 450 days were given. A prominent downward arrow labelled '35% RRR' appeared adjacent to the graph above the smaller much less

prominent figure 'ARR = 4.6% (p=0.016)'. The claim 'Among patients with an initial non-fatal cardiovascular event, Efient significantly reduced second events compared with clopidogrel' appeared alongside the graph.

AstraZeneca stated that the title and body of the bar chart referred to analysis of the secondary efficacy endpoint at 15 months yet Efient was recommended for use in adult patients up to a maximum of 12 months only. AstraZeneca alleged promotion beyond the licence, which was misleading.

With regard to the graph illustrating the endpoint of secondary CV events in the STEMI subgroup, AstraZeneca alleged that as the SPC recommended Efient for use in adult patients up to a maximum of 12 months only, the graph promoted beyond the licence and was misleading.

The Panel noted its general comments above about the recommended treatment period. The Panel further noted that there was no prominent mention on page 2 that treatment up to 12 months was recommended.

The Panel considered that the bar chart and its heading which referred to analysis at 15 months were inconsistent with the SPC and misleading. Breaches of the Code were ruled.

The Panel noted that Murphy *et al* looked at the recurrence of the primary endpoint events in TRITON-TIMI 38 with Efient compared with clopidogrel and concluded that Efient reduced both first and subsequent cardiovascular events at 15 months compared with clopidogrel in patients with ACS.

The Panel noted that the RRR claim for the advantage for Efient + ASA compared to clopidogrel + ASA was based on 15 month data. The Panel noted that the graph featured a dotted line at 12 months which represented the recommended treatment period. However by presenting the results at 15 months prominently the graph promoted the use of Efient for 15 months. This was misleading and inconsistent with the SPC recommendation. Breaches of the Code were ruled.

AstraZeneca noted that page 3 was headed 'Compared with Clopidogrel, Efient Offers:

- **Consistent platelet inhibition in healthy subjects**
- **Superior, long-lasting CV protection for 12 months of therapy**
- **No significant difference in non-CABG TIMI major bleedings in STEMI and diabetes patients'.**

The final bullet point again did not mention or reference the fact that in TRITON-TIMI 38 study, there were significantly worse bleeding rates seen with Efient vs clopidogrel. AstraZeneca alleged that this was not a balanced reflection of all available data, was misleading and did not reflect high standards.

In summary, AstraZeneca alleged that the leavepiece contained multiple misleading claims relating to efficacy and safety; promoted the off licence use of Efient; did not maintain high standards and did not accurately convey the incidence of serious side-effects seen with Efient by clearly providing the contradictory results of the TRITON-TIMI 38 study. Given the repeated nature and totality of these issues, and particularly with respect to the last and most serious point, AstraZeneca alleged a reduction in confidence in the industry as a whole in breach of Clause 2.

The Panel noted its previous comments about the differences in outcomes between safety data in Montalescot *et al* and TRITION-TIMI in point 1 above. Whilst the claim 'No significant difference in non-CABG TIMI major bleedings in STEMI and diabetes patients' was an outcome of the subgroup analyses it did not reflect the authors caveats nor was it placed in the context of the outcomes of the TRITON-TIMI study as a whole. This was not a fair reflection of the data. High standards had not been maintained in breach of the Code. Breaches of the Code were ruled.

With regard to the alleged breach of Clause 2 in relation to the leavepiece as a whole the Panel noted that Clause 2 was used as a particular sign of censure and reserved for such use. The Panel considered that given its rulings, particularly those in relation to the presentation of safety data above, the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

AstraZeneca UK Limited submitted a complaint about a four page Efient (prasugrel) leavepiece (ref UKEFF00714a) issued by Eli Lilly and Company Limited and Daiichi-Sankyo UK Limited. The leavepiece was headed 'How can you make a difference for your ACS-PCI Patients?'.

Efient, co-administered with acetylsalicylic acid (ASA), was indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) or ST segment elevation myocardial infarction (STEMI) undergoing primary or delayed percutaneous coronary intervention (PCI). Section 4.2 of the Efient summary of product characteristics (SPC), Posology and method of administration, stated that in patients with ACS who were managed with PCI, 'premature discontinuation of any antiplatelet agent, including Efient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless discontinuation of Efient is clinically indicated'.

The leavepiece in question was withdrawn on in May 2012 in order for changes to be made. AstraZeneca maintained that the withdrawal of the leavepiece was not due to successful inter-company dialogue. Daiichi-Sankyo and Lilly stated that various inter-company discussions about AstraZeneca's concerns were unsuccessful.

AstraZeneca alleged that the material was in breach of several clauses of the Code as it was inaccurate, misleading, played down major bleeding/safety considerations, promoted the off-label use of Efient beyond its maximum licensed duration of treatment, and as a result brought the industry into disrepute.

AstraZeneca stated that the leavepiece focussed on the STEMI subgroup of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombosis in Myocardial Infarction) study (pivotal registration study for Efient). AstraZeneca stated that the approach seen in the leavepiece was used extensively throughout promotional materials for Efient.

TRITON-TIMI 38 (Wiviott *et al*, 2001) was a Phase 3 trial involving patients with moderate to high risk ACS with scheduled PCI and compared Efient with clopidogrel (Plavix, a Sanofi product). All patients received ASA. The primary efficacy endpoint was death from cardiovascular causes, non fatal myocardial infarction (MI) or non fatal stroke. The key safety endpoint was major bleeding.

1 **Graph headed 'TRITON-TMI [*sic*] 38: pre-specified STEMI subgroup analysis of the primary efficacy endpoint* and key safety endpoint** at 15 months (n = 3,534)'.**

This appeared on page 1 of the leavepiece.

Page 1 had an orange band across the top on which was written in white type, 'Efient Proven Protection for ACS-PCI Patients Receiving Aspirin – Recommended for up to 12 Months'. Beneath, a prominent green band with larger white type bore the claim 'How can you make a difference for your ACS-PCI Patients?' followed by two sub headings 'STEMI Patients' and 'Help Give Your High Risk ACS-PCI Patients Superior Protection Against CV [cardiovascular] Events By Choosing Efient vs Clopidogrel'.

The graph was referenced as adapted from Montalescot *et al* (2009). The explanation for * in the graph title was given towards the bottom of page 1 as 'Efient significantly reduced the composite endpoint of CV death, non-fatal MI or non-fatal stroke vs. clopidogrel' and ** as 'No significant difference in incidence of non-CABG [coronary artery bypass graft surgery] related TIMI major bleedings vs. clopidogrel'.

The graph compared patients treated with clopidogrel + ASA and Efient + ASA in relation to CV death, MI, stroke and days from randomization. Non-CABG TIMI major bleeds were also compared for the two groups. The graph included data from 0 – 450 days from randomization and a vertical dotted line labelled 'Recommended length of treatment' indicated what appeared to be 365 days. On the right hand side of the graph was a prominent downward arrow labelled '21% RRR' [relative risk reduction]. Beneath this the actual risk reduction (ARR) was given in much smaller type 'ARR = 2.4%' p=0.0221' in favour of Efient in relation to CV death, MI, stroke. The comparison of non-CABG TIMI major bleeds did not show a statistically significant difference (p=0.6451).

COMPLAINT

AstraZeneca alleged that the title of the graph referred to analysis of the primary efficacy endpoint and key safety endpoint at 15 months. While Montalescot *et al* supported this graph, Section 4.2 of the Efient SPC stated that it was recommended for use in adult patients up to 12 months only. This therefore promoted Efient beyond the terms of its licence and was misleading in breach of Clauses 3.2 and 7.2.

Further the graph illustrated a subgroup analysis of the primary endpoint, including RRR and ARR figures based on outcomes at 15 months. A faint dotted line was presented at 12 months showing the recommended (and therefore licensed) maximum duration of treatment, however the graph continued far beyond this point. This off-licence promotion of Efient was compounded by there being no presentation of the actual data, for example ARR and RRR figures, at the 12 month point. This created the overwhelming impression that Efient could and should be used in excess of the maximum licensed duration of treatment and constituted misleading and off-label promotion. Breaches of Clauses 7.2 and 3.2 were alleged.

AstraZeneca alleged that the graph demonstrated a subgroup analysis of a key safety endpoint of non-CABG TIMI major bleeds at 15 months, contrary to the maximum licensed recommended duration of treatment of 12 months in breach of Clause 3.2. In addition, the information was presented as showing no significant difference between Efient and clopidogrel. While this might be the case in this specific subgroup, in the overall TRITON-TIMI 38 study Efient demonstrated significantly higher rates of non-CABG TIMI major bleeding (2.4% vs 1.8%, p=0.03), life threatening bleeding (1.4% vs 0.9%, p=0.01) and fatal bleeding (0.4% vs 0.1%, p=0.002). There was no mention of overall results anywhere within the leavepiece to provide the necessary context for clinicians to make an informed decision in relation to these serious outcomes. AstraZeneca alleged that this was therefore inaccurate, misleading and concerning as such selective representation of the data in such a misleading way, to the clear benefit of Efient, did not reflect high standards being maintained. Breaches of Clauses 7.2, 7.9 and 9.1 were alleged.

RESPONSE

Daiichi-Sankyo and Lilly referred to Section 4.2 of the Efient SPC, Posology and method of administration, which stated that 'A treatment of up to 12 months is recommended, unless the discontinuation of Efient is clinically indicated'. The companies also referred to Section 5.1, Pharmacodynamic properties, which mentioned the study endpoints which were reached after a median follow up period of '14.5 months (maximum of 15 months with a minimum of 6 months follow-up)'. Reference to use of Efient beyond 12 months was also included in Section 4.8, Undesirable effects, which stated 'Safety in patients with acute coronary syndrome undergoing PCI was evaluated in one clopidogrel-controlled study (TRITON) in which 6741 patients were treated with prasugrel (60 mg loading dose and 10 mg once daily maintenance dose) for a median of 14.5 months (5802 patients were treated for over 6 months, 4136 patients were treated for more than 1 year)'.

Daiichi-Sankyo and Lilly submitted that the above sections of the SPC were key in the assessment and determination of the complaint and supported the companies' position that the promotion of Efient was in accordance with the terms of its marketing authorization and not inconsistent with the particulars listed in its SPC.

The companies noted that AstraZeneca conceded that the references supported the depiction of the data in the leavepiece. Other than the alleged breach of Clause 2, the allegations were limited to promoting Efient in breach of Clause 3 and consequently Clause 7.

Daiichi-Sankyo and Lilly submitted that the reference to the STEMI sub-group analysis primary endpoint in the leavepiece was consistent with the Efient SPC which explicitly referred to a maximum 15 month follow-up period in Section 5.1 and, as a consequence, was not in breach of Clause 3.

Section 4.2 of the Efient SPC stated that the *recommended* duration of therapy is up to 12 months (emphasis added). This recommendation was clearly shown four times in the leavepiece. Firstly, at the top of page 1, in bold font ('Recommended for up to 12 months'); secondly, on the graph on page 1 with a dotted line at 12 months, beneath the words 'Recommended length of treatment'; thirdly, on the Kaplan Meier curves on page 2 entitled 'TRITON-TIMI 38: Landmark analysis of time from first event to second event by randomised therapy' with a dotted line at 12 months, beneath the words 'Recommended length of treatment' and finally in the prescribing information on the back page.

Daiichi-Sankyo and Lilly submitted that the leavepiece at issue emphasised, and majored on, the recommended duration of therapy. References to the 15 month follow-up period were, in all cases, both in accordance with the Efient marketing authorization and not inconsistent with the particulars of its SPC (Clause 3) and, further, were positively required in order not to mislead (Clause 7.2) and with respect to the graph adapted from Montalescot *et al* in order to provide a clear, fair and balanced representation of the data in accordance with Clauses 7.8 and 7.6.

Daiichi-Sankyo and Lilly submitted that the leavepiece was not misleading, either directly or by implication or as a practical matter. Efient was launched in the UK in April 2009; the TRITON-TIMI 38 data had been used since that time, and the graph from Montalescot *et al* had been used in promotional materials since at least April 2009, each without challenge. The companies were not aware of any health professionals suggesting that they had been misled by the graphical depiction of the pre-specified STEMI subgroup analysis of TRITON-TIMI 38, as alleged by AstraZeneca, or at all.

Daiichi-Sankyo and Lilly drew support for their view from the European Society of Cardiology's two guidelines, which each recommend Efient for no longer than 12 months. Furthermore, it was the companies' understanding that UK cardiology/PCI centres that had Efient on formulary typically have set the maximum length of treatment as 12 months. The companies were not aware of anyone setting a treatment duration of more than 12 months. In a handful of cases, maximum length of therapy had been set at a much shorter period – as little as 1 month or even just the loading dose.

Most importantly, the companies had no evidence to suggest that Efient was prescribed for longer than the recommended duration of therapy of 12 months.

PANEL RULING

The Panel noted that Section 4.2 of the Efient SPC, Posology and method of administration, stated that 'A treatment of up to 12 months is recommended, unless the discontinuation of Efient is clinically indicated …'. The graph at issue on page one of the leavepiece included a dotted line labelled 'Recommended length of treatment' at what appeared to be 365 days from randomization. The calculations for RRR and ARR appeared to be at the end of the study, ie 15 months.

The Panel noted that Section 4.8 (Undesirable effects) and 5.1 (Pharmacodynamic properties) of the Efient SPC referred to data at 14.5 months.

Clause 3.2 required that 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 the SPC. The Panel noted that the 15 month data was taken from the TRITON-TIMI 38 study, a pivitol registration study for Efient. Study visits were conducted at hospital discharge, at 30 days, 90 days and 3 months intervals thereafter for a total of 6 to 15 months.

The Panel noted that the prespecified subgroup analysis on patients with STEMI stated that the TRITON-TIMI 38 study was not prospectively designed or powered to show superiority of prasugrel over clopidogrel in the STEMI cohort alone. The subgroup analysis included detailed results for major efficacy and safety endpoints at 30 days and 15 months. The primary endpoint was CV death, non-fatal myocardial infarction or non-fatal stroke. The subgroup analysis had not been carried out at 12 months.

The Panel considered that the 15 month data would be of interest to prescribers. The SPC clearly referred to data beyond 12 months. The Panel considered that whilst it was acceptable to refer to the SPC data such references should be secondary to the statement at Section 4.2 of the SPC that treatment of up to 12 months was recommended.

The Panel noted that although the dotted line on the graph did not state the actual length of treatment, it could be approximately determined from the x axis. Neither the dotted line on the graph, nor the strapline at the top of the page which included the phrase 'Recommended for 12 months' were a visually prominent part of the overall page design. The Panel did not consider that the material on the page in question could be qualified by references to 12 month data in subsequent pages or in the prescribing

information as suggested by the companies. The supplementary information to Clause 7, general, stated, *inter alia*, that claims in promotional material must be capable of standing alone regards accuracy etc. The heading in question 'Triton-TMI 38: pre-specified STEMI subgroup analysis of the primary efficacy endpoint* and key safety endpoint** at 15 months (n-3, 534)' appeared in a highlighted green box and was visually prominent. It made no mention of the recommended duration of treatment. The graph beneath depicted and analysed data at 450 days. The Panel considered that the heading was misleading about the recommended treatment period and consequently inconsistent with the SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel noted that the graph made claims in relation to primary efficacy outcomes at 15 months. Other than the lines on the graph there was no mention or presentation of the actual ARR, or any other data, at 12 months.

The Panel noted that whilst a dotted line on the graph represented the recommended treatment period by presenting the efficacy and safety results at 15 months prominently with no data at 12 months the graph in effect promoted Efient for 15 months treatment. The 15 month data was not secondary to and or placed within the context of the 12 month recommended treatment period. This was misleading and inconsistent with the SPC recommendation. Breaches of Clauses 3.2 and 7.2 were ruled.

In relation to the results for non-CABG TIMI major bleeds the Panel noted that the subgroup analysis showed no significant difference between clopidogrel + ASA and Efient + ASA (p=0.6451). The overall outcome in this regard in TRITON-TIMI 38 was statistically significant in favour of clopidogrel + ASA for the key safety endpoint (2.4% vs 1.8% p=0.03 for non-CABG related TIMI major bleeding). Further, the data for life threatening bleeding (1.4% vs 0.9% p=0.01) and fatal bleeding (0.4% vs 0.1% p=0.002) were also in favour of clopidogrel + ASA. Montalescot *et al* stated that compared with clopidogrel, Efient was not associated with any significant increase in major bleeding, life-threatening bleeding or major or minor bleeding; however, formal testing for interaction was negative and these data should be interpreted with caution. In addition, differences in age (people presenting with STEMI were on average 2 years younger than non STEMI participants), the lower proportion of women, fewer diabetics and more smokers were differences that could account in part for the recorded low bleeding risk in the STEMI cohort.

The Panel considered that the allegation that the graph demonstrated a subgroup analysis of non-CAGB TIMI major bleeds at 15 months contrary to the maximum licensed duration of treatment of 12 months was covered by its ruling of a breach of Clause 3.2 as set out above.

The Panel noted that the overall safety results had not been included and it considered that the subgroup analyses had not been placed in context. The balance of the evidence had not been presented. Breaches of Clauses 7.2 and 7.9 were ruled. As the data related to safety endpoints the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

2 Bar Chart and Graph on Page 2

Page 2 was headed 'Make A Difference Now to Protect Their Future'. A bar chart followed by a graph were presented on this page.

The main heading to the bar chart was 'Confidence To Reduce The Risk Of Stent Thrombosis vs. Clopidogrel'. This was followed by the bar chart at issue which was headed 'TRITON-TIMI 38: pre-specified STEMI subgroup analysis of the secondary efficacy endpoint of stent thrombosis at 15 months (n=3,534)'. The bar chart was adapted from Montalescot *et al* and compared the incidence of definite or probable stent thrombosis of Efient + ASA (n=1769) and clopidogrel + ASA (n=1765). A prominent downward arrow labelled '42% RRR' appeared above the Efient bar. The ARR of 1.2%, p=0.0232 was given in less prominent smaller font on the left hand side of the bar chart. The claim 'Efient significantly reduced the risk of stent thrombosis compared with clopidogrel' appeared alongside the heading on the left hand side of the bar chart.

The second half of the page was headed 'Confidence to Reduce Recurrent Cardiovascular Events vs. Clopidogrel' beneath which was the heading 'TRITON-TIMI 38: Landmark analysis of time from first event to second event by randomised therapy (n=1,203)' to the graph.

The graph showed data adapted from Murphy *et al* (2008) which compared primary endpoint events (CV death, non-fatal MI or non-fatal stroke) for Efient + ASA and clopidogrel + ASA for 450 days from first event to second event or last follow-up. A dotted line was given on the graph to show recommended length of treatment. The results at 450 days were given. A prominent downward arrow labelled '35% RRR' appeared adjacent to the graph above the smaller much less prominent figure 'ARR = 4.6% (p=0.016)'. The claim 'Among patients with an initial non-fatal cardiovascular event, Efient significantly reduced second events compared with clopidogrel' appeared alongside the graph.

COMPLAINT

AstraZeneca stated that the title and body of the bar chart referred to analysis of the secondary efficacy endpoint at 15 months. Whilst Montalescot *et al* supported this graph, Efient was recommended for use in adult patients up to a maximum of 12 months only. AstraZeneca alleged promotion beyond the licence, which was misleading in breach of Clauses 3.2 and 7.2.

With regard to the graph illustrating the endpoint of secondary CV events in the STEMI subgroup, AstraZeneca alleged that whilst Murphy *et al* supported the graph, the SPC recommended Efient for use in adult patients up to a maximum of 12

months only. Similarly, to the graph on page 1, this promoted beyond the licence and was misleading in breach of Clauses 3.2 and 7.2.

RESPONSE

Daiichi-Sankyo and Lilly submitted that the pre-specified STEMI subgroup analysis was performed at the pivotal study endpoint after a maximum duration of therapy of 15 months. It was consistent with Section 5.1 of the SPC and the companies did not consider that including it in the leavepiece was a breach of the Code.

Similarly, the companies submitted that the reference to 15 months in relation to recurrent cardiovascular events was consistent with Section 5.1 of the Efient SPC. To further emphasise the recommended length of therapy (Section 4.2), a dotted line at 12 months beneath the words 'Recommended length of treatment' was included.

PANEL RULING

The Panel noted its general comments at Point 1 above about the recommended treatment period; references in the SPC to the data for 14.5 months; that prescribers would be interested in the 15 month data set out in Point 1 above and that references to treatment beyond 12 months should be secondary to and placed within the context of 12 month treatment period at section 4.2 of the SPC. The Panel further noted that there was no prominent mention on page 2 that treatment up to 12 months was recommended.

In relation to the bar chart the Panel noted that the RRR claim for the risk of stent thrombosis was based on 15 month data. The Panel considered that the bar chart and its heading which referred to analysis at 15 months were inconsistent with the SPC and misleading. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel noted that Murphy *et al* looked at the recurrence of the primary endpoint events in TRITON-TIMI 38 with Efient compared with clopidogrel and concluded that Efient reduced both first and subsequent cardiovascular events at 15 months compared with clopidogrel in patients with ACS.

The Panel noted that the RRR claim for the advantage for Efient + ASA compared to clopidogrel + ASA was based on 15 month data. The Panel noted that the graph featured a dotted line at 12 months which represented the recommended treatment period. However by presenting the results at 15 months prominently the graph promoted the use of Efient for 15 months. This was misleading and inconsistent with the SPC recommendation. Breaches of Clauses 3.2 and 7.2 were ruled.

3 Page 3 was headed 'Compared with Clopidogrel, Efient Offers:

- **Consistent platelet inhibition in healthy subjects**
- **Superior, long-lasting CV protection for 12 months of therapy**
- **No significant difference in non-CABG TIMI major bleedings in STEMI and diabetes patients'.**

COMPLAINT

AstraZeneca noted that the second bullet point highlighted that Efient should be used for 12 months. This bullet point was consistent with the SPC but in no way mitigated against the repeated off label promotion seen in the rest of the leavepiece with respect to duration of treatment.

The final bullet point again did not mention or reference the fact that in the main TRITON-TIMI 38 study, there were significantly worse bleeding rates seen with Efient vs clopidogrel. AstraZeneca alleged that this was not a balanced reflection of all available data, was misleading and did not reflect high standards, in breach of Clauses 7.2, 7.9 and 9.1.

In summary, AstraZeneca alleged that the leavepiece contained multiple misleading claims relating to efficacy and safety; promoted the off licence use of Efient; did not maintain high standards and did not accurately convey the incidence of serious side-effects seen with Efient by clearly providing the contradictory results of the main TRITON-TIMI 38 study. Given the repeated nature and totality of these issues, and particularly with respect to the last and most serious point, AstraZeneca alleged a reduction in confidence in the industry as a whole in breach of Clause 2.

In addition, AstraZeneca had also been made aware of a similar leavepiece, UKEFF00713, which focussed on the diabetes subgroup of the TRITON-TIMI 38 study. All of the issues and potential breaches of the Code highlighted with respect to UKEFF00714a also applied to this leavepiece. As previously mentioned, AstraZeneca believed that this approach had been adopted in a widespread manner across all promotional materials and asked the Authority to consider this when making its assessment.

AstraZeneca stated that despite unsuccessful inter-company dialogue, Daiichi-Sankyo and Lilly had indicated that they had withdrawn the leavepiece UKEFF00714a with immediate effect. AstraZeneca acknowledged this, though no broader agreement had been reached on the wide ranging concerns it had raised and which were detailed in its letter.

RESPONSE

Daiichi-Sankyo and Lilly stated that it appeared that AstraZeneca might have misunderstood the bullet point 'Superior, long-lasting CV protection for 12 months'. The statement was not a positive assertion/representation of Efient's licensed duration of therapy, it was intended to be a comparison of the two medicines, in compliance with Clause 7.

With regard to non-CABG TIMI major bleeding Daiichi-Sankyo and Lilly submitted that as an indication of efforts to amicably resolve the matter with AstraZeneca, it had offered to include the 15

month study endpoint non-CABG TIMI major bleeding results from the pivotal registration TRITON-TIMI 38 study in the leavepiece. As a consequence, the leavepiece in question was withdrawn to make changes.

Furthermore, the companies were prepared to emphasise even more clearly the recommended length of therapy of 12 months, whilst still depicting the 15 month pivotal registration trial data endpoints. Despite endeavours to make amends to the depiction of the graph, AstraZeneca was explicit in its position in that it 'would not find it acceptable to represent data for prasugrel beyond 12 months'. Daiichi-Sankyo and Lilly considered that there was no scientific or clinical merit to AstraZeneca's suggested approach of presenting 12 month post-hoc data from TRITON-TIMI 38: presenting data from a post-hoc analysis alone as demanded by AstraZeneca would be unacceptable and arguably in breach of Clause 7.8.

Daiichi-Sankyo and Lilly submitted that although not the subject of the original complaint, so far as was relevant, leavepiece UKEFF00713 was withdrawn in November 2011 as the item was not being used.

In the light of the above Daiichi-Sankyo and Lilly submitted that they had not breached the Code whether with respect to Clauses 2, 3 or 7, or at all.

With respect to the alleged breach of Clause 2, Daiichi-Sankyo and Lilly drew attention to the fact that the Montalescot graph was pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2009. No adverse comments were made about the graph. Although Daiichi-Sankyo and Lilly understood that such pre-vetting did not necessarily mean that the item complied with the Code, they believed that the MHRA, by endorsing the material, deemed the graph to be consistent with the Efient SPC. As a consequence the Daiichi-Sankyo's and Lilly's use of the leavepiece was not such as to be likely to bring discredit upon, or reduce confidence in, the pharmaceutical industry.

PANEL RULING

The Panel noted its previous comments about the differences in outcomes between safety data in Montalescot *et al* and TRITION-TIMI in point 1 above. Whilst the claim 'No significant difference in non-CABG TIMI major bleedings in STEMI and diabetes patients' was an outcome of the subgroup analyses it did not reflect the authors caveats nor was it placed in the context of the outcomes of the TRITON-TIMI study as a whole. This was not a fair reflection of the data. Breaches of Clauses 7.2 and 7.9 were ruled. High standards had not been maintained in breach of Clause 9.1.

With regard to the alleged breach of Clause 2 in relation to the leavepiece as a whole the Panel noted that Clause 2 was used as a particular sign of censure and reserved for such use. The Panel considered that given its rulings, particularly those in relation to the presentation of safety data in Points 1 and 3 above, the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

Complaint received **11 May 2012**

Cases completed **31 August 2012**

CASE AUTH/2514/6/12

VOLUNTARY ADMISSION BY BAXTER

Failure to certify an advertisement

Baxter voluntarily admitted that an advertisement for FEIBA (Factor VIII inhibitor bypassing agent) had been published in the UK version of the international journal, Haemophilia, prior to certification.

The detailed response from Baxter is given below.

The Panel noted that the advertisement at issue was published in the March 2012 edition of Haemophilia, ie before it was certified in April 2012. A breach of the Code was ruled as acknowledged by Baxter. The Panel noted that a draft advertisement had been submitted to the publisher prior to certification and considered that this could lead to problems if the submitted draft differed from the final approved advertisement. The Panel queried whether providing a draft advertisement was in effect issuing it as set out in the Code. The Panel considered that failing to certify prior to publication meant that high standards had not been maintained. A breach of the Code was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use. No breach of that clause was ruled.

Baxter Healthcare Limited made a voluntary admission to the Authority about an advertisement for its medicine FEIBA (Factor VIII inhibitor bypassing agent) published in the UK version of the international journal Haemophilia. FEIBA was indicated for the treatment of spontaneous or surgical bleeding in haemophilia and for prophylaxis in haemophiliacs with frequent joint bleeding.

COMPLAINT

Baxter submitted that earlier in 2012 it had reserved marketing space in Haemophilia for FEIBA following the publication of an important study.

In late January the publisher asked for draft artwork to allow it to begin typesetting and Baxter's agency supplied this. Baxter stated that the agency email made it very clear that this was a draft copy only and was not to be printed without written confirmation of approval from the agency or Baxter. Three days later the agency told the publishers that the copy was approved and that it could be released for publication which was not so; the advertisement was not finally approved by signatories until April.

Baxter submitted that as a draft copy was published prior to certification this was in breach of Clause 14.1.

Baxter stated that to prevent this from happening again it had reminded its marketing teams that the only acceptable evidence of material being released for use was the Code of Practice certificate complete with appropriate signatures. It was this and only this that should be supplied to agencies or publishers in order to release material.

When writing to Baxter the Authority asked it to respond in relation to the requirements of Clauses 9.1 and 2 as well as Clause 14.1 cited above.

RESPONSE

Baxter submitted that it had been a challenge to retrieve all correspondence in relation to this case; as its corporate email system automatically deleted messages after 90 days a number of emails were no longer available. While some communication was by email some took place by telephone and Baxter had to therefore rely on the memories of the individuals involved.

Baxter stated that concurrent with the review of the UK advertisement, its global team had paid for and created a separate FEIBA advertisement for the same journal. There were two versions of Haemophilia, for UK and international circulation. As the number of pages dedicated to one medicine in any issue of a journal was strictly limited by the Code, Baxter had insisted that the global advertisement should appear only in the international version of the journal. In addition the global advertisement would require UK approval as Haemophilia was a UK journal. This was agreed with the Baxter global team and its draft advertisement was submitted for review and approved, in accordance with UK policy, in late December 2011.

Baxter submitted that it was unable to definitively state why the agency informed the publisher that the advertisement at issue was approved. In Baxter's view, although it was difficult to provide evidence to support it, the issue arose due to human error and confusion around the submission of the two advertisements for the same medicine for different versions of the same journal with different areas of circulation.

Baxter stated that when it became aware of the error in early April 2012, key personnel were on leave and so it took until the middle of May for members of the medical team to investigate and establish exactly what happened; the team recommended that the company make a voluntary admission regarding a breach of Clause 14.1.

Baxter submitted that guidance to the marketing team referred to earlier had, to date, been verbal but it would be communicated in writing shortly.

Baxter considered that it was clear from its willingness to make this error public, and the

emphasis that it put on local approval of materials such as this by its European and global teams, that it was committed to high standards in all its activities. By acting in this way Baxter considered that it had upheld the reputation of, and increased confidence in, the pharmaceutical industry. The company denied a breach of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that emails provided by Baxter appeared to show that the advertisement at issue was published in the March 2012 edition of Haemophilia, ie before it was certified in April 2012. A breach of Clause 14.1 was ruled as acknowledged by Baxter. The Panel considered that submitting a draft advertisement to the publisher prior to certification could lead to problems if the submitted draft differed from the final approved advertisement. The Panel queried whether providing a draft advertisement was in effect issuing it as set out in Clause 14.1 of the Code. Taking all the circumstances into account the Panel considered that failing to certify prior to publication meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that although it first knew of the error in early April, it took Baxter until the middle of May to establish what had happened. The Panel noted that Baxter's investigation had not been helped by key personnel being on leave. The Panel further noted that in its response to the Authority in July, Baxter had submitted that although it had verbally reminded marketing teams that material could only be released with a Code of Practice certificate complete with appropriate signatures, no written guidance had yet been issued. In the Panel's view Baxter should have acted more quickly and decisively to ensure that its own staff and those of its agency had no doubt as to the correct procedures regarding the approval and certification of advertisements and their subsequent release for publication.

The Panel noted its comments above, however, it did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use. No breach of that clause was ruled.

Complaint received **13 June 2012**

Case completed **30 July 2012**

CASE AUTH/2516/6/12

ALLERGAN/DIRECTOR v MERZ

Breach of undertaking

Allergan alleged that a Bocouture (botulinum toxin type A) advertisement, issued by Merz Pharma UK and published in Cosmetic News, June 2012, breached the undertaking given in Case AUTH/2270/10/09. Allergan supplied Botox (botulinum toxin type A). The matter was taken up by the Director as the PMCPA was responsible for ensuring compliance with undertakings.

The advertisement featured a photograph of a vial of Bocouture and a vial of Botox side-by-side above which was the claim 'In glabellar frown lines, clinical studies suggest Bocouture vs Botox: Equal Potency 1:1 Clinical Conversion Ratio'. Below the vials was a thick blue horizontal line beneath which was the statement in smaller black font 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'. This statement and the claim for equal potency were referenced to the Bocouture summary of product characteristics (SPC) June 2010. The claim for a 1:1 clinical conversion ratio was referenced to Sattler *et al* (2010).

Allergan alleged that the advertisement and Merz's ongoing promotional campaign would lead prescribers to conclude that Bocouture and Botox were interchangeable in terms of potency units and delivered equivalent clinical results.

Allergan noted that the current Bocouture SPC (6 March 2012) stated 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.' Allergan was concerned that the advertisement cited the June 2010 SPC which Merz knew would imminently change to remove the statement prominently featured in the advertisement.

The Bocouture 50U SPC (and that of Merz's product Xeomin (botulinum toxin type A)) was changed after Allergan had highlighted to the regulatory authorities potential patient safety concerns with the wording in the Bocouture 50U and Xeomin 50U SPCs. Any reference to equal potency in the Bocouture SPC had been removed.

The statement regarding a 1:1 dosing ratio in Section 4.2 of the Xeomin 50U SPC had been removed. The information from non-inferiority studies in Section 5.1 of the Xeomin 50U SPC was specifically about patients with blepharospasm or cervical dystonia. As previously established, non-inferiority studies did not support claims of equivalence.

The SPCs for Botox 50U, 100U and 200U stated 'Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan units are different from other botulinum toxin preparations.'

Allergan alleged that the claim '1:1 Clinical Conversion Ratio' and the visual of Bocouture and Botox vials side-by-side emphasised a direct 1:1 equivalence/conversion of the two products. In significantly smaller font was the SPC statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.'

Health professionals would assume that Bocouture and Botox were equally potent and could be converted 1:1. Allergan was concerned about Merz's promotion of this 1:1 clinical conversion ratio between Bocouture and Botox. No 'dosing conversion' occurred or should be implied from the non-inferiority study conducted by Merz with its toxin (Sattler *et al*). Allergan submitted that a significant patient safety risk existed with prescribers encouraged to transfer information from one label to another product.

Allergan noted that in Case AUTH/2270/10/09 it was ruled that the results of a non-inferiority study could not be used to claim equivalence. In that case Merz submitted that it had no data to support a claim that Xeomin was equivalent to Botox and this was still so. Therefore, Allergan alleged that the visuals, which implied equivalence/equipotency and the claim '1:1 Clinical Conversion Ratio' between Bocouture and Botox, (ie equivalence), breached the undertaking given in Case AUTH/2270/10/09.

The detailed response from Merz is given below.

The Panel noted that in Case AUTH/2270/10/09 it had considered a complaint from Allergan that the claim by Merz that Xeomin was 'At least as effective as Botox with a similar safety profile' without appropriate context and qualification did not accurately reflect the available evidence and was misleading. Allergan had submitted that to make the claim 'At least as effective as', Merz needed further evidence to confirm equivalent efficacy and clinically relevant superiority. The claim at issue was referenced to Benecke *et al* (2005) and Roggenkamper *et al* (2006) both of which were non-inferiority studies. The Panel considered that there was a difference between showing non-inferiority and showing comparability and that the claim that Xeomin was 'At least as effective as Botox' did not reflect the available evidence. It implied possible superiority of Xeomin and was misleading as alleged; breaches of the Code were ruled. Upon appeal by Merz, the Appeal Board noted Merz's submission that it had no data upon which to claim that Xeomin was equivalent to Botox. The Appeal Board stated that in its view, the claim 'At least as effective as' not only implied equivalence but also possible superiority which was misleading. The Appeal Board did not consider that the claim could

be substantiated by the available data and the Panel's rulings were upheld.

The Panel noted that the material now at issue in Case AUTH/2516/6/12 was different to that at issue in Case AUTH/2270/10/09. In Case AUTH/2270/10/09 the comparison at issue had been between Xeomin and Botox; the comparison now at issue was between Bocouture and Botox. Bocouture and Xeomin, however, were the same product but with different indications.

The Panel noted that the advertisement now at issue had also been at issue in Case AUTH/2496/4/12 in which Allegan had made similar allegations. The Panel's ruling in that case, that the undertaking in Case AUTH/2270/10/09 had not been breached, was overturned upon appeal by Allergan. The Panel considered that the Appeal Board's ruling of a breach of undertaking applied to the case now before it, Case AUTH/2516/6/12. The Panel thus ruled a breach of the Code. The Panel ruled a further breach as high standards had not been maintained.

The Panel noted that it was extremely important that companies complied with undertakings; to do otherwise brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel further noted that there was still no data upon which to base a claim that Botox and Bocouture were clinically equivalent. The Panel was concerned to note that although the advertisement in question had been withdrawn following changes to the Bocouture SPC, Cosmetic News subsequently published it in error. The Panel considered that companies must have robust procedures to ensure that, when required and for whatever reason, materials were withdrawn from all relevant parties including agencies and publishers. Although Merz had reviewed its processes for ensuring publishers used only current and approved advertisements, the Panel considered that the circumstances were such that Merz had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Allergan Limited complained about a Bocouture (Botulinum toxin type A) advertisement (ref 1075/BOC/DEC/2011/JH) issued by Merz Pharma UK Ltd which was published in Cosmetic News, June 2012. Allergan supplied Botox (Botulinum toxin type A).

The matter was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The advertisement featured a photograph of a vial of Bocouture and a vial of Botox side-by-side. Above the vials was the claim in bold, blue font 'In glabellar frown lines, clinical studies suggest Bocouture vs Botox: Equal Potency 1:1 Clinical Conversion Ratio'. This claim and the photograph took up over half of the advertisement. Below the vials was a thick blue horizontal line beneath which was the statement in smaller black font 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'. This statement and the claim for equal potency were referenced to the Bocouture summary of product characteristics (SPC) June 2010. The claim for a 1:1 clinical conversion ratio was referenced to Sattler *et al* (2010).

COMPLAINT

Allergan alleged that the advertisement and Merz's ongoing promotional campaign had been designed to lead prescribers to conclude that Bocouture and Botox were interchangeable in terms of potency units and delivered equivalent results in clinical practice.

The 'Equal Potency' claim was referenced to the Bocouture SPC, June 2010. The current SPC for Bocouture (which was updated on 6 March 2012) stated:

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

Allergan was concerned that the advertisement which was published in the June 2012 edition of Cosmetic News, prepared in February 2012, referred to an old SPC which Merz knew would imminently change to remove the statement prominently featured in the advertisement.

The UK Bocouture 50U SPC (and that of Merz's product Xeomin (Botulinum toxin type A)) was changed following Allergan's communication to the Pharmacovigilance Working Party (PhVWP) highlighting potential patient safety concerns with the wording in the Bocouture 50U and Xeomin 50U SPCs. Any reference to equal potency in the Bocouture SPC had been removed.

Allergan pointed out that the statement regarding 1:1 dosing ratio in Section 4.2 of the Xeomin 50U SPC, Posology and method of administration, had been removed. The Xeomin 50U SPC still contained information regarding its non-inferiority studies (Section 5.1, Pharmacodynamic properties) but this was in relation to specific patients ie those with blepharospasm or cervical dystonia. As previously established, non-inferiority studies did not support claims of equivalence.

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

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

Allergan noted Merz's use of the claim '1:1 Clinical Conversion Ratio' and visual of Bocouture and Botox vials side-by-side and alleged that this was clearly designed to emphasise a direct 1:1 equivalence/ conversion of the two products. The claim 'In glabellar frown lines, clinical studies suggest' was included. Less prominently and in significantly smaller font was the statement from the SPC 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.'

Allergan considered that health professionals would take away the message that Bocouture and Botox

were equally potent and could be converted 1:1. The promotion by Merz of this 1:1 clinical conversion ratio between Bocouture and Botox was of significant concern. No 'dosing conversion' occurred or should be implied from the non-inferiority study conducted by Merz with its toxin (Sattler *et al*).

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

Allergan noted the ruling in Case AUTH/2270/10/09 that the results of a non-inferiority study could not be used to claim equivalence. Merz's own submission in that case was that it had no data to support a claim that Xeomin was equivalent to Botox. This was still so and Merz had not published any new clinical data to support a claim of equivalence for either Xeomin or Bocouture. Therefore, Allergan alleged that the visuals, which implied equivalence/equipotency and the claim '1:1 Clinical Conversion Ratio' between Bocouture and Botox (ie equivalence), were a breach of the undertaking given in Case AUTH/2270/10/09 and as such were in breach of Clause 25.

When writing to Merz, the Authority asked it to respond in relation to Clauses 2 and 9.1 in addition to Clause 25 cited by Allergan.

RESPONSE

Merz noted that in Case AUTH/2270/10/09 it was found in breach of the Code for claiming that Xeomin was 'At least as effective as Botox with a similar safety profile'. The Panel considered that the claim implied possible superiority of Xeomin vs Botox which was not supported by the available data. The breach was upheld upon appeal.

Merz further noted that in Case AUTH/2496/4/12, claims of 'Equipotent' or 'Equal Potency' were ruled on by the Panel in the context of Case AUTH/2270/10/09 for the advertisement in question (ref 1075/BOC/DEC/2011/JH) and no breaches of Clauses 2, 9.1 or 25 were found.

Merz therefore considered that the advertisement now at issue did not breach the undertaking given in Case AUTH/2270/10/09 and was not in breach of Clauses 2, 9.1 or 25.

Merz submitted that the advertisement in question was withdrawn from circulation (due to the update to the Bocouture SPC) and the last Bocouture insertion was March. No further Bocouture advertising was planned until an updated advertisement had been developed (April and May editions did not contain the advertisement in question). Merz had two full page advertisements booked for the June edition for its dermal fillers, Radiesse and Belotero. On 8 June an updated Bocouture advertisement was sent to the journal for all future use. Cosmetic News erroneously printed the June edition with Radiesse and the old Bocouture advertisement (instead of Belotero). Merz had reviewed its processes for ensuring publishers used only current and approved advertisements.

The withdrawal of the advertisement at issue had already been captured in the undertaking (signed 27 June 2012) to comply with the Panel's ruling in Case AUTH/2496/4/12.

PANEL RULING

The Panel noted that in Case AUTH/2270/10/09 it had considered a complaint from Allegan that the claim by Merz that Xeomin was 'At least as effective as Botox with a similar safety profile' without appropriate context and qualification did not accurately reflect the available evidence and was misleading. Allergan had submitted that to make the claim 'At least as effective as', Merz needed further evidence to confirm equivalent efficacy and clinically relevant superiority. The claim at issue was referenced to Benecke *et al* (2005) and Roggenkamper *et al* (2006) both of which were non-inferiority studies. The Panel considered that there was a difference between showing non-inferiority and showing comparability and that the claim that Xeomin was 'At least as effective as Botox' did not reflect the available evidence. It implied possible superiority of Xeomin and was misleading as alleged and breaches of the Code were ruled. Following an appeal by Merz, the Appeal Board noted Merz's submission that it had no data upon which to claim that Xeomin was equivalent to Botox. The Appeal Board stated that in its view, the claim 'At least as effective as' not only implied equivalence but also possible superiority which was misleading. The Appeal Board did not consider that the claim could be substantiated by the available data and the Panel's rulings were upheld.

The Panel noted that the material now at issue in Case AUTH/2516/6/12 was different to that at issue in Case AUTH/2270/10/09. In Case AUTH/2270/10/09 the comparison at issue had been between Xeomin and Botox; the comparison now at issue was between Bocouture and Botox. Bocouture and Xeomin, however, were the same product but with different indications – Bocouture was indicated for the temporary improvement in the appearance of glabellar frown lines whilst Xeomin was for the symptomatic treatment of blepharospasm, cervical dystonia and post-stroke spasticity of the upper limb.

The Panel noted that the advertisement now at issue had also been at issue in Case AUTH/2496/4/12. In that case, Allegan had similarly alleged that the claims for 'Equal Potency' and '1:1 Clinical conversion ratio' were in breach of the undertaking given in Case AUTH/2270/10/09. The Panel's ruling of no breach of the Code was overturned following an appeal by Allergan. The case was considered in July (ie after the advertisement had reappeared in the June edition of Cosmetic News) and the Appeal Board in its ruling stated:

> 'The Appeal Board noted that the undertaking in [Case AUTH/2270/10/09] related to a claim that not only implied equivalence but also possible superiority; its ruling had been made on both aspects. In the current case, Case AUTH/2496/4/12, Allergan's allegation regarding a breach of undertaking, the subject of the appeal, related only to claims of equivalence.

The Appeal Board noted that to date there was still no data to show whether Xeomin/Bocouture was equivalent to Botox/Vistabel. Now, as when the ruling in Case AUTH/2270/10/09 was made, there were only non-inferiority studies which showed that the medicines were no worse than each other by a clinically acceptable pre-specified margin.

Turning to Case AUTH/2496/4/12, the Appeal Board considered that the Bocouture advertisement (ref 1075/BOC/DEC/2011/JH) claim 'In glabellar frown lines, clinical studies suggest' followed by 'Bocouture vs Botox:', 'Equal potency' and '1.1 Clinical Conversion Ratio' together with the visual beneath of a vial of each of the medicines side-by-side, implied to prescribers that the two products were clinically equivalent and that unit for unit they were interchangeable. The Appeal Board considered that although the claim at issue was not the same as that in Case AUTH/2270/10/09, it was sufficiently similar with regard to a claim for 'equivalence' for it to be covered by the undertaking previously given. The Appeal Board thus ruled a breach of Clause 25. The appeal on this point was successful.

The Appeal Board noted that the Bocouture advertisement included the statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin' and the Xeomin advertisement similarly included the statement 'Always prescribe by brand, unit doses are not interchangeable'. These statements were referenced to the respective products' SPCs and in both advertisements they appeared in a less prominent position and smaller font than the claims and visuals that implied clinical equivalence. The Appeal Board considered that implying that the products were clinically equivalent and hence interchangeable was contrary to statements in the SPCs. The Appeal Board considered that this raised possible patient safety concerns.

The Appeal Board considered that as Merz had no data on which to base the implied claims of clinical equivalence and as it had breached its undertaking and assurance in Case AUTH/2270/10/09 it had failed to maintain high standards and it had thus brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled breaches of Clauses 9.1 and 2. The appeal on this point was successful.'

The Panel considered that the Appeal Board's ruling of a breach of Clause 25 applied to the case now before it, Case AUTH/2516/6/12. The Panel thus ruled a breach of that clause. The Panel considered that as the undertaking had not been complied with, high standards had not been maintained. A breach of Clause 9.1 was ruled.

With regard to the alleged breach of Clause 2, the Panel noted that it was extremely important that companies complied with undertakings; to do otherwise brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel further noted that there was still no data upon which to base a claim that Botox and Bocouture were clinically equivalent. Although the claim for a 1:1 clinical conversion ratio between Bocouture and Botox was referenced to Sattler *et al*, this was a non-inferiority study and so did not substantiate the claim. The Panel was concerned to note that although the advertisement in question had been withdrawn following changes made to the Bocouture SPC, Cosmetic News subsequently published it in error. The Panel considered that companies must have in place robust procedures to ensure that, when required and for whatever reason, materials were withdrawn from all relevant parties including agencies and publishers. The Panel noted Merz's submission that it had reviewed its processes for ensuring publishers used only current and approved advertisements. Nonetheless, the Panel considered that the circumstances were such that Merz had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **15 June 2012**

Case completed **24 August 2012**

CASE AUTH/2517/6/12

ANONYMOUS v PROSTRAKAN

Promotion of Adcal D_3 Caplet

An anonymous, non-contactable complainant who signed his/her complaint 'An aggrieved Surgery' complained about certain practices by ProStrakan and its representatives in relation to Adcal-D_3 Caplet (calcium carbonate and colecalciferol).

The complainant recently saw a sales representative and manager who had promoted the latest addition to the Adcal range, Adcal-D_3 Caplet.

The complainant noted that the same information was used to promote other products in the range. The representative and manager assured the complainant that the data in the detail aid and leavepieces were relevant to Adcal-D_3 Caplet and the product was included in the clinical trials cited. This was alleged to be misleading as the studies were almost a decade old and Adcal-D_3 Caplet could not be included as it was not a year old.

The complainant stated that his/her surgery had used ProStrakan's switch programme to swap patients from other calcium supplements to Adcal-D_3 Caplet based on misleading data in the material. However the complainant and his/her colleagues considered that they had compromised their patients by unwittingly believing the data and the 'carrot' that was dangled in the form of a switch programme. The surgery would review those patients that had been inconvenienced by the switching of medication.

The detailed response from ProStrakan is given below.

The Panel noted ProStrakan's submission that the claims made for Adcal-D_3 Caplet were based on Chapuy *et al* and Tang *et al*. Neither included any of the Adcal range of products. However, the results of Chapuy *et al* were detailed in Section 5.1, Pharmacodynamic properties, of the Adcal-D_3 Caplet summary of product characteristics (SPC). The 18 month efficacy data to support the UK marketing authorization application for Adcal-D_3 Caplet were derived from Chapuy *et al*.

The Panel noted that page 3 of the detail aid was entitled 'The NEW Adcal-D_3 Caplet – offering your patients an effective dose of calcium and vitamin D_3'. The page gave the results of Chapuy *et al* in relation to the use of 1200mg elemental calcium and 800IU vitamin D_3 daily in significantly reducing hip fractures and non-vertebral fractures vs placebo over 18 months. Page 4 of the detail aid had the same title and noted that a meta-analysis (Tang *et al*) concluded that daily doses of at least 1200mg calcium and 800IU vitamin D_3 had been shown to achieve a better therapeutic effect than lower doses. Similar information appeared in the leavepiece. The Panel noted that the adult and elderly daily dose of Adcal-D_3 Caplet (two tablets twice a day) delivered a total daily dose of 3000mg of calcium carbonate (equivalent to 1200mg of calcium) and 800IU of colecalciferol (equivalent to 20mcg vitamin D_3).

The Panel considered that the detail aid and leavepiece were clear that the efficacy data included was for 1200mg calcium and 800IU vitamin D_3 daily rather than specifically for Adcal-D_3 Caplet. They were not misleading in that regard. The Panel noted that the marketing authorization for Adcal-D_3 Caplet was granted on the basis of established use including Chapuy *et al* data. The Panel considered that in principle Chapuy *et al* and Tang *et al* could substantiate claims for Adcal-D_3 Caplet and, on this narrow ground, such claims were not misleading. No breaches of the Code were ruled.

The Panel noted that the complainant bore the burden of establishing his/her case on the balance of probabilities. The Panel noted that ProStrakan had denied the allegations but it was unable to identify those concerned and respond in detail to the allegations. The Panel noted that it was difficult in cases involving discussions between representatives and a health professional to know exactly what had transpired. A judgement had to be made on the available evidence. The Panel did not consider that the complainant had shown that, on the balance of probabilities, the representative and his/her manager had failed to maintain a high standard of ethical conduct in relation to claims about the product. No breaches of the Code were ruled.

The Panel noted its rulings above about the representatives but nonetheless was concerned about the briefing material. Whilst it was made clear in the detail aid briefing document that Adcal-D_3 was not included in Tang *et al* no such caveat was applied to Chapuy *et al*. The Panel considered that it was particularly important to give clear instructions to representatives about this matter. The failure to make any relevant comment in relation to Chapuy *et al* followed by unequivocal statements that Adcal-D_3 was not used in Tang *et al* was misleading by omission. The specific briefings on the two studies had not provided the representatives with a clear message in this regard. Consequently the briefing material was likely to lead to a breach of the Code and a breach was ruled. This did not amount to a failure to maintain high standards and no breach, including Clause 2, was ruled.

The Panel noted ProStrakan's submission that it did not offer a switch service but that it did support a therapy review service for patients who might be at risk of osteoporosis. The Panel noted that the Code permitted therapy reviews, providing they enhanced

patient care, or benefited the NHS whilst maintaining patient care.

The Panel noted that the sales force briefing for the review service stated that the service was offered as an aid to improve patient care with respect to the provision of appropriate calcium and vitamin D supplementation. The service comprised of a review conducted within GP practices, which aimed to identify patients who might have calcium and/or vitamin D deficiency and therefore might be at risk of developing osteoporosis.

The briefing stated that the review would focus on patients: receiving bisphosphonates to assess the need for adjunctive calcium/vitamin D therapy; with a Read code of osteoporosis who were not receiving necessary treatment; with a prior fragility fracture and those who were elderly, housebound or institutionalised. The service might also include, if requested, a review of patients in line with an enhanced service for osteoporosis.

The service was open to any GP practice which was computerised and was not to be linked in any way to promotional activity or be carried out in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine. Representatives were instructed that if they had included a product detail in a call then the service should only be discussed in brief and another call arranged to discuss it in detail. If a doctor had volunteered that he wished to switch any patients to a ProStrakan product then the service could not be offered as this would be seen as facilitating a switch programme. The briefing provided detailed steps for the representative to undertake once a practice had agreed to the service and the protocol was signed. The representative introduced the pharmacist carrying out the review to the practice but then the representative was to leave and have no further interaction with the pharmacist. There could be no promotional activity in the location on the day of the therapy review or for three days before or after.

The Panel noted that, without details of the surgery, ProStrakan was unable to respond in detail to allegations about the offer and implementation of the service at the surgery in question. The Panel further noted that the complainant had produced no evidence in relation to the allegation that the service provided by ProStrakan was a switch service and/or that it was offered as such. The Panel did not consider that the calcium and vitamin D therapy review service was a switch service as alleged nor was it offered as such. The service was not an inducement to prescribe, supply, administer, recommend, buy or sell a medicine and no breach was ruled including Clause 2.

An anonymous, non-contactable complainant who signed off his/her complaint 'An aggrieved Surgery' complained about certain practices by ProStrakan Limited and its representatives which the complainant considered unethical. The complaint was in relation to Adcal-D_3 Caplet (calcium carbonate and colecalciferol) which was indicated as an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition.

COMPLAINT

The complainant stated that he/she recently saw a sales representative and his/her manager who had promoted the latest addition to the Adcal range (Adcal-D_3 Caplet).

However, on closer inspection of the promotional material the complainant noted that it seemed to be the same information used to promote other products from the range. When the complainant questioned the representative and manager he/she was assured that the data in the detail aid and leavepieces were relevant to Adcal-D_3 Caplet and the product was included in the respective clinical trials cited in those materials.

Upon further investigation the complainant considered that the information in ProStrakan's promotional material and the conduct of its representatives was misleading. The studies cited in the promotional material were almost a decade old; so how could Adcal-D_3 Caplet be included in the data when it was not a year old?

The complainant stated that his/her surgery had used ProStrakan's switch programme to swap patients from other calcium supplements to Adcal-D_3 Caplet based on misleading data in the promotional material. However the complainant and his/her colleagues considered that they had compromised their patients by unwittingly believing the data that was put before them and the 'carrot' that was dangled in the form of a switch programme. The surgery had spoken to the local prescribing advisor and would review those patients that had been inconvenienced by the switching of medication. When writing to ProStrakan, the Authority asked it to respond in relation to the requirements of Clauses 7.2, 7.4, 15.2, 15.9, 18.1, 18.4, 9.1 and 2.

RESPONSE

ProStrakan submitted that the complaint concerned data to support promotional claims for Adcal-D_3 Caplet. As the complainant did not stipulate which claims or clinical papers were at issue, ProStrakan assumed that the complaint related to the two key papers which supported the efficacy claims for the product. The other references used in the Adcal-D_3 Caplet materials related either to competitor products or to the therapy area more broadly.

ProStrakan stated that the promotional claims for Adcal-D_3 Caplet were supported by Chapuy *et al* (1992) and Tang *et al* (2007). No data from the use of any of the products in the Adcal range, including Adcal-D_3 Caplet, was included in Chapuy *et al*. However, the results of this study featured prominently in Section 5.1, Pharmacodynamic properties, of the Adcal-D_3 Caplet summary of product characteristics (SPC), which stated:

> 'Strong evidence that supplemental calcium and vitamin D_3 can reduce the incidence of hip and other non-vertebral fractures derives from an 18 month randomised placebo controlled study in 3270 healthy elderly women living in nursing homes or apartments for elderly people. A

positive effect on bone mineral density was also observed.'

The section then discussed the results of Chapuy *et al* in more detail. Indeed, all of the 18 month efficacy data to support the successful marketing authorization application in the UK for Adcal-D_3 Caplet (a bibliographic filing based on established use) were derived from Chapuy *et al*.

ProStrakan submitted that as the regulatory authorities clearly accepted the approach that strong evidence of efficacy could be based on established use and an assumption of a class effect, the Tang *et al* meta-analysis was also relevant to the promotion of Adcal-D_3 Caplet as it included calcium/vitamin D doses equivalent to that of the recommended dose of Adcal-D_3 Caplet, ie 1200mg of elemental calcium and 800IU of colecalciferol daily.

ProStrakan stated that it had not claimed that Adcal-D_3 Caplet or the Adcal product ranges were included in the studies discussed above. Indeed, the Adcal product range was developed at the single commercialised dosage strength because of the work completed by Chapuy *et al* to meet the therapeutic needs identified by this research. As such this study provided the pivotal efficacy data for the UK marketing authorization approval for Adcal-D_3 Caplet and the Adcal product range.

ProStrakan also disputed the complainant's claim that the data was 'old'. Whether data was 'old' was a relative assessment, and one that must be made with consideration to the other information available. ProStrakan's products, and the claims for its products, were supported by the best clinical evidence. Indeed, the efficacy data referred to in the current SPC was approved by the regulatory authorities as recently as last year. The data from Chapuy *et al* had proven satisfactory for licensing purposes for Adcal-D_3 Caplet and the rest of the Adcal range. Given the therapy area, new trials arose infrequently and given the available evidence base, further placebo controlled trials would not receive ethics committee approval given the known benefits of therapy vs the morbidity and mortality risk associated with hip fracture. Tang *et al* provided a more recent and valuable meta-analysis that added significant statistical value to the claims.

ProStrakan submitted that the complainant was correct in that the clinical data used to support Adcal-D_3 Caplet was the same as that included in the materials for the rest of the Adcal range. This was because all these marketing authorization applications took the form of a bibliographic filing based on established use including the Chapuy *et al* efficacy data.

A copy of the sales force briefing document (Key Account Team Brief – Adcal-D_3 Caplet Campaign (ref M004/0018)) was provided which ProStrakan submitted was the brief most likely to be in use when the alleged complaint occurred. This document had been withdrawn from use in line with the undertaking submitted in relation to Case AUTH/2481/2/12. The current briefing differed only in relation to the line concerning the Halal status of the product that was at issue in that case.

ProStrakan stated that this briefing document covered the key materials used to promote Adcal-D_3 Caplet (the detail aid (ref M004/0001), doctor leavepiece (ref M004/0002) and pharmacy leavepiece/sales aid (ref M004/0003)) and gave general information regarding the campaign. While this document covered the key papers cited above, the sales team was not instructed to claim that Adcal-D_3 Caplet (or the Adcal range in general) was included in any of the relevant studies. Indeed, on two occasions the brief explicitly stated that representatives should be clear that the Adcal range was not part of these trials. On page 6 of the document the briefing covered the sales aid to be used in calls. It stated:

'The RCTs [Randomised Controlled Trials] included in the study included varying doses of calcium and/or vitamin D_3 products, and Adcal-D_3 was not used in the trials. It is important that you do not insinuate that Adcal-D_3 was used in any of the trials involved in this meta-analysis.'

This point was later reiterated on page 10 in relation to the pharmacy leavepiece.

A copy of the detail aid and the doctor leavepiece were provided. ProStrakan noted that whilst the clinical trials mentioned above were referenced in both items neither made claims that any member of the Adcal range was included in the studies.

With respects to the complainant's reference to a 'switch programme', ProStrakan clarified that it did not offer a switch service. It did support a therapy review service to facilitate the review of patients who might be at risk of osteoporosis using a practice-agreed protocol specifically designed in conjunction with each participating practice. This service had been reviewed and certified in line with the Code, and was supplied in compliance with it.

A copy of the briefing document used to train representatives on the provision of the therapy review service (ProStrakan Sales Force Briefing: Calcium and Vitamin D Therapy Review Service (ref NPR/0153)) was provided. ProStrakan stated that this document was clear about the strict conditions which governed the provision of the service. ProStrakan's therapy review service was offered to any computerised practice that requested it.

ProStrakan submitted that considerable effort had been made to ensure that the conditions under which the service was offered were in line with the Code. This brief explicitly mentioned the way in which this service was differentiated from switch programmes:

'If the doctor has volunteered that he wishes to switch any patients onto a ProStrakan product, the service cannot be offered, as this would be seen as facilitating a switch programme, which would constitute a breach of the Code.'

ProStrakan stated that the brief also detailed the other regulations it had instituted to ensure that the service was offered in a compliant manner. The service must only be discussed in detail by the sales team in a separate, non-promotional, call.

Representatives were not permitted to be in the practice when the review took place (with the exception of introducing the pharmacist on day one) and no promotional activity could take place three days before or after the review.

In order to further investigate the claims made by the complainant ProStrakan had interviewed key members of staff responsible for the promotion and commercialisation of Adcal-D_3 Caplet. As the complainant was associated with a GP surgery the interviews focused on the key account team (KAT) which worked in primary care. All of the KAT regional managers were interviewed, as were randomly selected representatives from each region. The sales director responsible for the promotion of all ProStrakan products in the UK, was also interviewed. The marketing manager for the Adcal range and the manager responsible for commercial operations in the UK (senior vice president commercial Northern Europe) were also involved.

ProStrakan noted that although the complainant had referred to the national sales manager, no-one in the company had that job title. The equivalent position (ie the individual responsible for sales teams nationally) was the sales director who had not been out on a field visit with a KAT representative in the last six months.

ProStrakan submitted that a number of the interviewees (both management and representatives) commented on how rare it was for a customer to ask questions about the clinical studies which supported Adcal-D_3 Caplet. Most had found that health practitioners were more than happy with the clinical data supporting calcium/vitamin D supplementation. As the Adcal range was well established, and the clinical data consistent throughout the range, most customers met by ProStrakan's teams were already clear on this data.

ProStrakan stated that in advance of specific questions regarding the complaint each interviewee was questioned on the clinical data underpinning the Adcal-D_3 Caplet campaign and the regulations regarding therapy review. Each could reference the key studies and a number spontaneously mentioned that the Adcal range was not included as part of the studies. All were clear on the procedure for offering a therapy review. Considerable surprise was expressed that a customer would still refer to a switch programme. This term was not used by ProStrakan employees.

ProStrakan submitted that the interviews did not identify the individuals referred to by the complainant. The complainant had offered no clues as to his/her identity or location and his/her anonymity meant that no further detail could be sought. ProStrakan had found no evidence that its representatives had acted in contravention to the Code and so the company denied a breach of Clause 15.2.

Further, ProStrakan considered that the briefing documents which instructed its teams on how they should conduct themselves were sufficiently clear and did not advocate a course of action that was likely to lead to a breach of the Code. ProStrakan thus denied a breach of Clause 15.9.

ProStrakan stated that neither the interviews nor the material review identified claims that were not capable of substantiation. The clinical data which underpinned the Adcal-D_3 Caplet campaign clearly corroborated the claims made in it, and was of sufficient quality to support the campaign. ProStrakan argued that neither Clauses 7.2 nor 7.4 had been breached.

ProStrakan noted that its therapy review service offered the practices which requested it the chance to have an independent, third party company review the treatments provided to key patient groups in order to raise the standards of care in relation to osteoporosis. This therapy review service was reviewed and provided under the provision for medical and educational goods and services in the Code. Indeed, ProStrakan had developed appropriate supporting materials to ensure that the integrity of this service to medicine was maintained and that it was provided in a manner that complied with the Code. The brief that accompanied the service clearly stated that it must not be offered to those who had decided to use ProStrakan's products so as to ensure that no confusion could occur on this score. ProStrakan therefore denied a breach of either Clause 18.1 and 18.4.

ProStrakan submitted that high standards had been upheld, and no breach of Clause 9.1 had occurred. As a consequence it also considered that a ruling of a breach of Clause 2 was not justified.

ProStrakan stated that it would value the opportunity to investigate the matter more fully, but without any further detail on the complainant or the employees involved, this was not possible. Whilst it respected the complainant's anonymity, ProStrakan noted that an anonymous complaint limited its ability to investigate allegations in detail and deprived the company of the standard reassurances provided by the PMCPA that the complainant had been asked to declare any conflict of interest.

ProStrakan provided copies of the protocol for the calcium and vitamin D therapy review service (ref NPR/0178) and the specific briefings on Chapuy *et al* (ref M001/1417) and Tang *et al* (ref M001/1422).

PANEL RULING

The Panel noted ProStrakan's submission that the promotional claims made for Adcal-D_3 Caplet were based on Chapuy *et al* and Tang *et al*. The Tang *et al* meta-analysis had included Chapuy *et al*. Neither Tang *et al* nor Chapuy *et al* included any of the Adcal range of products. However, the results of Chapuy *et al* were detailed in Section 5.1, Pharmacodynamic properties, of the Adcal-D_3 Caplet SPC. All of the 18 month efficacy data to support the marketing authorization application in the UK for Adcal-D_3 Caplet were derived from Chapuy *et al*.

The Panel noted ProStrakan's submission that the clinical data used to support claims for Adcal-D_3 was identical to that used for the rest of the Adcal range

because the marketing authorization applications were each a bibliographic filing based on established use, including the Chapuy *et al* data.

The Panel noted that page 3 of the Adcal-D_3 Caplet detail aid (ref M004/0001) was entitled 'The NEW Adcal-D_3 Caplet – offering your patients an effective dose of calcium and vitamin D_3'. The page then went on to detail the results of Chapuy *et al* which confirmed the use of 1200mg elemental calcium and 800IU vitamin D_3 daily in significantly reducing hip fractures and non-vertebral fractures vs placebo over 18 months. Page 4 of the detail aid had the same title and noted that a meta-analysis (Tang *et al*) concluded that daily doses of at least 1200mg calcium and 800IU vitamin D_3 had been shown to achieve a better therapeutic effect than lower doses. Similar information appeared on page 2 of the doctor leavepiece (ref M004/0002). The Panel noted that the adult and elderly daily dose of Adcal-D_3 Caplet (two tablets twice a day), as stated in the SPC, delivered a total daily dose of 3000mg of calcium carbonate (equivalent to 1200mg of calcium) and 800IU of colecalciferol (equivalent to 20mcg vitamin D_3).

Given the above, the Panel considered that the detail aid and doctor leavepiece were clear that the efficacy data included was for 1200mg calcium and 800IU vitamin D_3 daily rather than specifically for Adcal-D_3 Caplet. The Panel did not consider that either the detail aid or the doctor leavepiece were misleading in that regard and no breach of Clause 7.2 was ruled. The Panel noted that the marketing authorization for Adcal-D_3 Caplet was granted on the basis of established use including Chapuy *et al* data. The Panel considered that in principle Chapuy *et al* and Tang *et al* could substantiate claims for Adcal-D_3 Caplet and, on this narrow ground, such claims were not misleading. No breach of Clauses 7.2 and 7.4 were ruled.

The Panel noted that the complainant was anonymous and non-contactable thus further queries could not be raised with him/her. The complainant bore the burden of establishing his/her case on the balance of probabilities. The Panel noted that ProStrakan had denied the allegations but without details of the individuals concerned and/or the surgery it was unable to identify those concerned and respond in detail to the allegations. The complainant alleged that when questioned about the data used in promotional material the representative and national sales manager assured him/her that the data was relevant to Adcal-D_3 Caplet and the medicine was included in the studies cited. The Panel noted that it was difficult in cases involving discussions between representatives and a health professional to know exactly what had transpired. A judgement had to be made on the available evidence. The Panel did not consider that the complainant had shown that, on the balance of probabilities, the representative and his/her manager had failed to maintain a high standard of ethical conduct in relation to claims about the product. No breach of Clause 15.2 was ruled.

The Panel noted that the briefing document 'Key Account Team Brief – Adcal-D_3 Caplet Campaign' (ref M004/0018) stated that pages 3 and 4 of the detail aid focused on the results of two studies in which 1200mg calcium and 800IU vitamin D_3 produced statistically significant results on fragility fractures; page 3 summarised Chapuy *et al* and page 4 featured the key outcomes of the Tang *et al* meta-analysis. The briefing document noted that the randomized controlled trials included in Tang *et al* used varying doses of calcium and/or vitamin D_3 products and Adcal-D_3 was not used in the trials and stated 'It is important that you do not insinuate that Adcal-D_3 was used in any of the trials involved in this meta-analysis'. It was not, however, made clear that Chapuy *et al* was included in this meta-analysis nor did a separate, similar statement appear in relation to page 3 and Chapuy *et al*. The same instruction appeared later in the briefing document in relation to the two leavepieces and was similarly limited to Tang *et al*. Neither of the specific briefings on the two studies clearly and unambiguously stated that Adcal-D_3 was not used in the relevant study. The Panel noted its rulings above about the representatives but nonetheless was concerned about the briefing material. Whilst it was made clear in the detail aid briefing document that Adcal-D_3 was not included in Tang *et al* no such caveat was applied to Chapuy *et al*. The Panel considered that it was particularly important to give clear instructions to representatives about this matter given that the marketing authorization was granted on the basis of existing use. The Panel considered that the failure to make any relevant comment in relation to Chapuy *et al* followed by unequivocal statements that Adcal-D_3 was not used in Tang *et al* was misleading by omission. The specific briefings on the two studies had not provided the representatives with a clear message in this regard. The Panel considered that consequently the briefing material was such that it was likely to lead to a breach of the Code; a breach of Clause 15.9 was ruled.

The Panel did not consider that the briefing document amounted to a failure to maintain high standards and ruled no breach of Clauses 9.1. No breach of Clause 2 was consequently ruled.

Turning to the alleged switch programme, the Panel noted ProStrakan's submission that it did not offer a switch service but that it did support a therapy review service to facilitate the review of patients who might be at risk of osteoporosis. The Panel noted that Clause 18.4 permitted the provision of medical and educational goods and services, including, *inter alia*, therapy reviews, providing they enhanced patient care, or benefited the NHS whilst maintaining patient care, subject to the provisions of Clause 18.1.

The Panel noted that the sales force briefing for the review service (ref NPR/0153) stated that the service was offered as an aid to improve patient care with respect to the provision of appropriate calcium and vitamin D supplementation. The service comprised of a review conducted within GP practices, the aim of which was to identify patients who might have calcium and/or vitamin D deficiency and therefore might be at risk of developing osteoporosis. The review aimed to improve patient care and to benefit the practice and the NHS.

The briefing noted that the review would focus on patients: receiving bisphosphonates to assess the need for adjunctive calcium/vitamin D therapy; with a Read code of osteoporosis who were not receiving necessary treatment; with a prior fragility fracture and those who were elderly, housebound or institutionalised. The service might also include, if requested, a review of patients in line with either the directed enhanced service for osteoporosis (England) or with a local enhanced service or similar.

The Panel noted from the sales force briefing that the service was open to any GP practice which was computerised. It stated that the service must not be linked in any way to promotional activity or be carried out in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine now or in the future. Representatives were instructed that if they had included a product detail in a call then the service should only be discussed in brief and another call arranged to discuss it in more detail. If a doctor had volunteered that he wished to switch any patients to a ProStrakan product then the service could not be offered as this would be seen as facilitating a switch programme. The briefing provided detailed steps for the representative to undertake once a practice had agreed to the service and the protocol was signed. The representative introduced the pharmacist carrying out the review to the practice but then the representative was to leave the practice and have no further interaction with the pharmacist. There could be no promotional activity in the location on the day of the therapy review or for three days before or after.

The service protocol (ref NPR/0178), which was provided to each participating practice prior to the service commencing, stated that it was not linked to the use of any particular product and that the independent prescriber retained full control over the entire process and could amend, remove or add any aspect. Section 2 of the protocol detailed the patient selection criteria as noted in the briefing above and section 3 provided an alphabetical list of 14 calcium and vitamin D formulations. A box at the bottom of the list stated 'Other – please specify'. The review pharmacist would, *inter alia*, search the GP clinical system to identify patients as determined and authorized in the protocol then review each patient file. Summary sheets were prepared by the pharmacist for review, amendment and where necessary authorization by the GP before any changes were made to the patient's electronic records. The summary sheets were left with the practice.

The Panel noted that, without details of the surgery, ProStrakan was unable to respond in detail to allegations about the offer and implementation of the service at the surgery in question. The Panel further noted that the complainant had produced no evidence in relation to the allegation that the service provided by ProStrakan was a switch service and/or that it was offered as such. The Panel did not consider that the calcium and vitamin D therapy review service was a switch service as alleged nor was it offered as such and in that regard it ruled no breach of Clause 18.4. The service was not an inducement to prescribe, supply, administer, recommend, buy or sell a medicine and no breach of Clause 18.1 was ruled.

The Panel noted its rulings above and consequently ruled no breach of Clauses 9.1 and 2.

Complaint received **18 June 2012**

Case completed **5 September 2012**

CASE AUTH/2519/6/12

GENERAL PRACTITIONER v LILLY

Conduct of representative

A general practitioner complained about the unprofessional and unacceptable conduct of a representative from Lilly who had visited his surgery with a poster. Following instructions from his/her manager, the representative insisted on photographing members of the practice team underneath the poster.

The complainant stated that the representative's aim was to get 10 photographs of doctors and nurses with the poster in order to win a prize. The complainant refused to go along with this, as did a nurse. The complainant stated that the representative then became quite shirty and insistent so the complainant left. Three other staff members had since complained that they were also unhappy but had their photographs taken rather than make a fuss.

The detailed response from Lilly is given below.

The Panel noted that the poster was derived from Lilly's diabetic peripheral neuropathic pain (DPNP) foot symptom assessment tool and asked readers if they were diabetic and ever got odd or painful feelings in their legs or feet. The poster was designed to raise awareness about the symptoms of DPNP. Health professionals might want to display the poster in the waiting room. There was no mention on the poster or the briefing document that representatives were to take photographs of a health professional with the poster.

The Panel noted Lilly's submission that one sales manager had implemented a customer engagement incentive competition for his/her team. This sales team was briefed using a presentation entitled 'The Wall of Pain Hall of Fame Competition' which explained that the competition was 'A project to engage representatives and customers to display the Foot Screening Poster in appropriate target surgeries' and 'An opportunity to enable the representatives to learn other functionalities of the iPad'. The aim of the competition was for each representative to have the poster displayed in 10 practices and to photograph the poster 'with or without your customer'. If 10 surgeries per representative was reached then the team would be rewarded with 'our usual cocktails'. One point would be awarded for each photograph of a poster in situ without a health professional and two points if a GP or nurse was in the photograph. Prizes were a £25 cinema voucher for the representative with the most points and a further £25 cinema voucher for the representative with the best, most amusing photograph including a GP or nurse. There was further reference to the 'bonus prize' of cocktails if each representative reached 10 surgeries. The presentation gave instructions on how to take and email the photographs. There was no mention of any professional discussion of the poster with health professionals or of the benefit of the poster to patient care. There was no guidance about when/whether to request a photograph nor to respect the wishes of the surgeries/health professionals in this regard.

The Panel was concerned that the name of the competition, 'The Wall of Pain Hall of Fame Competition', trivialised a painful complication of diabetes. The representatives were encouraged to amass points by placing the poster in as many surgeries as possible and provide photographic evidence of their success. There was no professional element to the competition.

The Panel considered that neither the sales manager who had instigated the competition nor the primary care sales team (which, on the balance of probabilities, included the representative at issue) that took part in the competition had maintained a high standard of ethical conduct. The presentation on the competition advocated a course of action that was likely to lead to a breach of the Code and high standards had not been maintained. Breaches of the Code were ruled, as acknowledged by Lilly.

As Lilly had not been provided with information to identify the representative it was impossible to determine precisely what had occurred. The Panel thus ruled no breach of the Code in relation to the allegations about how the representative in question had described the competition and the representative's behaviour.

The Panel noted Lilly's submission that the sales manager at issue had acted independently and that Lilly had not briefed its sales force to undertake the activities at issue. However, the Panel considered that the sales manager's encouragement of representatives to collect points by taking photographs of health professionals and rewarding this with cinema vouchers and cocktails was an activity that demeaned both the health professionals and the representatives and in that regard was likely to bring discredit upon the pharmaceutical industry. A breach of Clause 2 was thus ruled. This ruling was appealed by Lilly

The Appeal Board noted that the sales manager had independently devised the competition with the aim of engaging his team to encourage display of the foot screening poster in surgeries so that patients might be better informed about DPNP and report symptoms. The Appeal Board considered that greater awareness of foot problems would be helpful to diabetics.

The Appeal Board was extremely concerned that someone as senior as a sales manager, who had line management responsibility, considered it acceptable to direct his team to try to include a GP or a nurse in photographs in surgeries to gain points towards

winning cinema vouchers and cocktails. The Appeal Board was also concerned that additional points would be given to photographs with the health professional and a prize was to be given for the most amusing photograph including a health professional. Participation in the photographs was potentially demeaning to heath professionals.

The Appeal Board considered that the sales manager had displayed very poor judgement and the competition as a whole was distasteful.

The Appeal Board noted that on receipt of the complaint Lilly had ceased the competition and no prizes had been awarded. Lilly had not condoned the behaviour of the sales manager and had accepted the Panel's rulings of breaches of the Code. The poster competition had been initiated and devised by a single sales manager without the company's knowledge or approval and it had taken place in a limited geographical area.

Although Lilly had been ruled in breach of the Code, including failure to maintain a high standard, the Appeal Board considered, on balance, that the activities did not amount to a breach of Clause 2. This clause was a sign of particular censure and was reserved for such circumstances. Thus no breach of Clause 2 was ruled. The appeal was thus successful.

A general practitioner complained about the conduct of a representative from Lilly who had visited his surgery and, apparently following instructions from his/her manager, insisted on photographing members of the practice team underneath a poster which he/she had brought to the complainant's surgery.

COMPLAINT

The complainant said that the representative's aim was to get 10 mugshots of doctors and nurses with the poster in order to win a prize. The complainant refused to go along with this, as did a nurse, as he considered it a potential infringement of his human rights. The complainant stated that the representative then became quite shirty and insistent so the complainant left. Three other staff members had since complained that they were also unhappy to have had their photographs taken but did so rather than make a fuss.

The complainant considered the conduct of the representative was very unprofessional and unacceptable. Lilly representatives were no longer welcome at his practice.

When writing to Lilly the Authority asked it to respond in relation to the requirements of Clauses 15.2, 15.9, 9.1 and 2.

RESPONSE

Lilly submitted that it was extremely concerned about the complainant's allegations since it found the alleged behaviour entirely unacceptable and would not condone it.

Lilly noted that the complaint contained very limited information to help it identify the source of the behaviour and alleged activity, since the representative and location were not identified and there was no information about the therapeutic area involved or the content of the poster.

Lilly submitted that the alleged activity was not one upon which it had centrally briefed its sales force but it had identified activity in one primary care sales team (with a total of 12 sales representatives), which appeared to be relevant.

Lilly believed that the poster at issue was material derived from an enlarged version of a diabetic peripheral neuropathic pain (DPNP) foot symptom assessment tool introduced to the sales force by email in March 2012, with full, approved briefing instructions for its use. Lilly also produced posters based on, and as a derivation of, the tool for patient waiting rooms. The poster had clear instructions on the reverse and explained that it was for a health professional to display in an area where patient materials were available. The sales force was told about the poster during a conference call in March 2012 and it was rolled out using Lilly's automated system for ordering sales materials. No additional briefing instructions were issued to the sales team for this poster at that time as it had clear instructions on the reverse on its intended use as a DPNP patient information poster to provide to health professionals.

Lilly submitted that the briefing and information on the reverse of the poster comprised the central Lilly briefing material used to tell representatives how to use it. Lilly maintained that the instructions were clear and that it had not issued additional guidance regarding the use of the poster or instructed any sales teams to deviate from these instructions.

Lilly stated that it appeared that the sales manager for one of its primary care sales teams comprising 12 sales representatives had of his/her own accord implemented a customer engagement incentive competition around the poster for the sales representatives in his/her team, intending to engage representatives and customers to display the poster. Lilly understood that the sales manager told the sales team about the competition at a regional meeting and it was intended that the competition would run in the summer. The presentation set out how the competition would work. The sales manager confirmed that he/she had instructed the sales team to get customers' permission before photographing them and that if a customer did not wish to be photographed they should not proceed. This instruction was not included in the written presentation.

Lilly submitted that it was most concerned about the competition and accepted that it was entirely inappropriate. Accordingly, upon becoming aware of these activities, Lilly took immediate steps to stop the competition. The sales manager at issue informed all sales representatives in his/her team by text that the competition would cease with immediate effect and followed up each text with

either a personal telephone call or face-to-face meeting the same day. The competition ceased on 25 June 2012. Lilly confirmed that apart from the sales team involved, no other representatives were involved in the competition.

Lilly maintained that it had provided its representatives with detailed briefing material in compliance with the Code in this instance. It had also appropriately trained its representatives on both the Code and privacy requirements. The activities which were the subject of this complaint were those of one isolated primary care sales team/sales representative acting on his/her own and contrary to Lilly's central briefing instructions.

Consequently, Lilly accepted that there had been a breach of Clauses 15.9 and 9.1 and undertook to retrain the sales team at issue on both the requirements of the Code and on privacy requirements. It had already applied internal processes to follow-up with the responsible sales manager.

Lilly noted that the complainant had not agreed to be identified to Lilly, nor had he/she identified the representative who was the subject of the complaint or provided evidence to support his/her allegations. Notwithstanding this, Lilly had tried to identify the representative in question by requesting further information from the sales team about their knowledge of this complaint and any background information. Despite these efforts, Lilly had not been able to identify the representative and was therefore unable to properly investigate his/her conduct or respond to the allegations made concerning his/her behaviour.

Whilst Lilly accepted that the activities of one sales team was not of the high standard required by the Code, it denied that these activities were of such a serious nature as to constitute a breach of Clause 2 of the Code. They were isolated and did not constitute multiple and cumulative breaches of a similar or serious nature in the same therapeutic area within a short period of time; they did not prejudice patient safety and/or public health; neither did they involve inducements to prescribe, inadequate action leading to a breach of undertaking or promotion prior to the grant of a marketing authorization.

Lilly submitted that it had taken immediate steps both to try and investigate the actions of the representative involved and to stop the activities in question as soon as it knew of them. It had also undertaken to retrain the sales team involved. Lilly thus did not consider that it had brought discredit upon, or reduced confidence in, the pharmaceutical industry and denied a breach of Clause 2.

PANEL RULING

The Panel noted Lilly's submission that it considered the poster at issue was that derived from the DPNP foot symptom assessment tool. The associated briefing instructed the representatives how a health professional could use the tool; either by providing the patient with a dry wipe marker pen to write on the document and wipe clean afterwards or for the health professional to stick to the wall of their consulting room as a reminder of the questions they should ask patients to help identify DPNP. There was no mention in the briefing document of the poster at issue.

The Panel noted that the poster asked the reader if they were diabetic and ever got odd or painful feelings in their legs or feet such as burning, pins and needles, freezing. The poster had a note on the back for health professionals explaining, *inter alia*, that the poster was designed to raise awareness among patients about the symptoms of DPNP. It went on to state that the health professional might want to display the poster in an area of his/her clinic in which other patient materials were available such as the waiting room. There was no mention of the representative taking a picture of the poster and a health professional.

The Panel noted Lilly's submission that a sales manager for a primary care team had implemented a customer engagement incentive competition for his/her sales team around the poster. This sales team were told about the competition in May by way of a 15 slide presentation entitled 'The Wall of Pain Hall of Fame Competition'. The second slide of the presentation explained that the Wall of Pain Hall of Fame was 'A project to engage representatives and customers to display the Foot Screening Poster in appropriate target surgeries'. It was also 'An opportunity to enable the representatives to learn other functionalities of the iPad'. The third slide explained that the aim of the competition was for each representative to have the foot pain poster on display in 10 practices and photograph the poster 'with or without your customer'. If 10 surgeries per representative was reached then the team would be rewarded with 'our usual cocktails'. The fourth slide noted that one point would be awarded for each photograph of a poster in situ without a GP or nurse in the photograph, and two points if a GP or nurse was in the photograph. The fifth slide stated that the prizes were a £25 cinema voucher for the representative with the most points at the end of the competition and a further £25 cinema voucher for the representative with the best, most amusing photograph including a GP or nurse. This slide again referred to the 'bonus prize' of cocktails if each representative reached 10 surgeries. The remaining 10 slides of the presentation instructed the representatives on how to take a photograph with their iPad and then email it. There was no mention of any professional discussion of the poster with health professionals or of the benefit of the poster to patient care. There was no guidance about when/whether to request a photograph nor to respect the wishes of the surgeries/health professionals in this regard.

The Panel noted that the aim of the competition, to engage representatives and customers to display the poster, was not necessarily unacceptable but any such competition must comply with the Code. The Panel was concerned that the name of the competition, 'The Wall of Pain Hall of Fame Competition', trivialised a painful complication of diabetes. The representatives were encouraged to amass points by placing the poster in as many surgeries as possible and provide photographic evidence of their success. There was no professional element to the competition.

The Panel considered that neither the sales manager who had instigated the competition nor the primary care sales team (which, on the balance of probabilities, included the representative at issue) that took part in the competition had maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled. The presentation on the competition advocated a course of action that was likely to lead to a breach of the Code and a breach of Clause 15.9 was ruled, as acknowledged by Lilly. High standards had not been maintained and a breach of Clause 9.1 was ruled, as acknowledged by Lilly. These rulings were accepted by Lilly.

The Panel noted that the complainant had also made allegations about what the representative had said and his/her conduct. As Lilly had not been provided with the identity/location of the representative/surgery it had been unable to respond to this aspect of the complaint. Consequently it was impossible to determine precisely what had occurred. The Panel thus ruled no breach of Clause 15.2 in relation to the allegations about how the representative in question had described the competition and the representative's behaviour. This ruling was not appealed.

The Panel noted Lilly's submission that the sales manager at issue had acted independently and that Lilly had not briefed its sales force to undertake the activities at issue. However, the Panel considered that the sales manager's encouragement of representatives to collect points by taking photographs of health professionals and rewarding this with cinema vouchers and cocktails was an activity that demeaned both the health professionals and the representatives and in that regard was likely to bring discredit upon the pharmaceutical industry. A breach of Clause 2 was thus ruled. This ruling was appealed by Lilly

APPEAL BY LILLY

Lilly noted that the Panel had ruled no breach of Clause 15.2 in relation to the anonymous allegations made about the representative. The ruling of a breach of Clause 2 related only to the behaviour of one sales manager and the internal competition that he organised (together, the activity). Lilly did not condone or support the activity and accepted the Panel's ruling of breaches of Clauses 9.1, 15.2 and 15.9. In appealing the Panel's ruling of a breach of Clause 2, Lilly submitted that it had made no suggestion whatsoever that it supported or condoned the activity: it did not.

Lilly noted that the supplementary information to Clause 2 stated that a ruling of a breach of Clause 2 '… is a sign of particular censure and is reserved for such circumstances'. The guidance went on to provide examples of the types of activity which were likely to be in breach of Clause 2; all of them were clearly very serious.

Lilly submitted that the basis of its appeal was that it accepted that the activity breached Clauses 9.1, 15.2 and 15.9 but the activity was not of such a serious nature so as to bring discredit upon the industry; it was initiated by, and limited to, one sales manager acting independently, in breach of the company's policies and procedures, in a lapse of judgement. It was a single and isolated activity on a very limited scale, it was not a multiple or cumulative breach. It did not impact patient safety or care, involve an inducement to prescribe, relate in any way to promotion outside the marketing authorization nor was it otherwise of such a serious nature so as to bring discredit upon the industry. As such, Lilly's appeal centred on the severity of the censure.

Lilly focussed on the following key areas:

1 **It was an isolated activity, not representative of Lilly's activities** – this activity was an isolated activity, initiated by one sales manager acting on his own. The sales manager committed a serous error of judgement, although Lilly believed that he/she had had the best of intentions (see point 4 below); it was not an activity that Lilly initiated centrally, encouraged or on which it briefed its sales force and it was entirely unrepresentative of Lilly's activities. In short, it was unauthorised.

2 **Full accountability for the actions of its employees** – Lilly took full responsibility for the action of its employees. Once identified (through a country-wide investigation, immediately instigated following receipt of the complaint), this activity was stopped straightaway and corrective action taken. Details were provided. Lilly retrained the sales manager and the twelve sales representatives in his team on the requirements of the Code in addition to their usual refresher training. Lilly would carry out additional ethics and compliance retraining, directed at all sales managers in Lilly UK's human health business units on both the requirements of the Code and compliance matters generally to avoid a repetition.

   In taking this action Lilly had taken ultimate accountability for the activity.

3 **Appropriate level of censure given the limited scale of the activity** – Lilly gave detailed information about its sales force in the UK. The sales team reporting to the sales manager in question amounted to only a very small percentage of Lilly's UK sales force. From the point of view of Lilly's customer base this activity at most had the potential to impact less than 1% of GP practices in the UK. It had a very limited scale, whether considered geographically, as a percentage of Lilly's sales force, or as a percentage of health professionals it had the potential to touch as a whole; this activity was therefore entirely unrepresentative of the overall direction and activity performed by Lilly's large sales force with the vast majority of its customer base.

4 **Patient benefit/intent** – DPNP was a painful complication of diabetes, which was unreported by patients and had a relatively low rate of diagnosis/treatment. Lilly submitted that it was for this reason it had placed a good deal of focus in trying to support health professionals around assessment of DPNP by producing tools which facilitated detection and diagnosis of the condition, ultimately having a significant patient benefit. Lilly's view, having questioned the sales manager, was that, despite the lapse of

judgement, the intentions had been good – the competition forming part of the activity was not to demean health professionals (or, indeed, sales representatives, as suggested), but to try and encourage them to display a poster in their surgeries which might lead to patients reporting their symptoms to the health professional and ultimately to diagnosis and better care.

5 **Additional context of wider Lilly work in the DPNP therapy area** – Lilly noted the Panel's comments that the activity 'trivialised' a painful complication of diabetes and potentially demeaned health professionals. Lilly submitted that it promoted a National Institute for Health and Clinical Excellence (NICE) recommended medicine in the therapy area of DPNP and as such took very seriously both the disease area and the impact that it could have on patients' lives. Lilly provided a significant level of support, tools and education to health professionals to help them in their assessment of their patients in accordance with guidelines and best practice. Focussing on the narrow context of the single and isolated activity did not provide a fair representation of the company's wide ranging support to health professionals and their patients suffering from DPNP. Examples of the support tools Lilly provided in this therapy area (and which were already in use by the sales manager and his team, among others) were provided, including 'A Tool for the Initial Assessment of Foot Pain Among People with Diabetes'; 'Addressing the burden of diabetic peripheral neuropathic pain: Improving detection in primary care' together with its briefing document and 'Looking after your feet'.

Upon receiving the initial complaint, Lilly submitted that it immediately launched a full investigation – despite the difficulty of the complaint being anonymous and with limited information. Upon identifying what it submitted to be the cause, ie an internal activity initiated by one primary care sales manager (who, despite good intentions, exercised poor judgement), acting without authority, Lilly stopped it immediately. Prior to responding to the PMCPA Lilly took corrective action with the relevant employee. Lilly had immediately acknowledged accountability for the actions of its employees and pre-emptively accepted that there were breaches of the Code. The activity concerned was not in any way centrally driven or endorsed by Lilly, but was a single and isolated activity and not widespread (whether considered geographically, as a percentage of Lilly's sales force, or as a percentage of the health professionals that it had the potential to touch as a whole). The activity did not in any way provide a true representation of Lilly's support and commitment to this very important therapeutic area.

Accordingly, Lilly submitted that a ruling of a breach of Clause 2, which was a sign of particular censure, was not justified in this case.

RESPONSE FROM THE COMPLAINANT

The complainant was happy with the explanations and that the activity at issue could not happen again. The complainant accepted that Lilly might wish this case to be seen as an isolated incident and it was up to the relevant bodies to decide what importance, if any, was put on the episode overall, for which he had nothing to add.

APPEAL BOARD RULING

The Appeal Board noted that the sales manager had offered an incentive of cinema vouchers and possibly cocktails to his team. This appeared to be inconsistent with the Lilly representatives' response to a question at the appeal hearing that incentives were national not local.

The Appeal Board noted that the sales manager had independently devised the competition with the aim of engaging his team to encourage display of the foot screening poster in surgeries so that patients might be better informed about DPNP and report symptoms. The Appeal Board considered that greater awareness of foot problems would be helpful to diabetics. The Appeal Board noted, however, that the sales manager's training slides were titled 'The Wall of Pain Hall of Fame Competition'.

The Appeal Board was extremely concerned that someone as senior as a sales manager, who had line management responsibility, considered it acceptable to direct his team to try to include a GP or a nurse in photographs in surgeries to gain points towards winning cinema vouchers and cocktails. The Appeal Board was also concerned that additional points would be given to photographs with the health professional and a prize was to be given for the most amusing photograph including a health professional. Although participation in the photographs appeared to be optional it was potentially demeaning to heath professionals.

The Appeal Board considered that the sales manager had displayed very poor judgement and the competition as a whole was distasteful.

The Appeal Board noted that on receipt of the complaint Lilly had ceased the competition and no prizes had been awarded. Lilly had not condoned the behaviour of the sales manager and had accepted the Panel's rulings of breaches of Clauses 9.1, 15.2 and 15.9. The poster competition had been initiated and devised by a single sales manager without the company's knowledge or approval and it had taken place in a limited geographical area.

Although Lilly had been ruled in breach of the Code, including failure to maintain a high standard, the Appeal Board considered, on balance, that the activities did not amount to a breach of Clause 2. This clause was a sign of particular censure and was reserved for such circumstances. Thus no breach of Clause 2 was ruled. The appeal was thus successful.

Complaint received **7 June 2012**

Case completed **6 September 2012**

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM & LILLY

Alleged promotion of Trajenta

A general practitioner alleged that an educational meeting jointly sponsored by Boehringer Ingelheim and Eli Lilly & Company to discuss referrals to the renal clinic and the management of kidney health and care, was the disguised promotion of Trajenta (linagliptin). The two companies co-promoted Trajenta (linagliptin) for the treatment of type 2 diabetes.

The complainant submitted that when referring to the management of diabetic complications the speaker made unfettered reference to the key marketing messages for Trajenta, ie no modification of dosage necessary in diabetics with renal disease, that Trajenta represented an unmet need in such patients compared with other medicines in the same class, the inference that other medicines in the class were suboptimal and represented an unacceptable safety profile and that Trajenta improved compliance by virtue of its single dosage strength. No counterpoints were offered in favour of the other medicines in the class.

The detailed response from the two companies is given below.

The Panel noted Boehringer Ingelheim and Lilly's submission that the meeting was organised at the behest of a GP partner who requested an educational meeting to discuss the referral of patients with renal impairment from primary to secondary care. A Lilly representative co-ordinated the meeting and the speaker (suggested by the GP partner) had agreed to be the sole speaker. A Boehringer Ingelheim representative had attended.

The speaker had created his own slide deck and the Panel noted from the speaker/consultant agreement submitted by the companies that the title of the meeting was 'When to refer to the Renal Clinic'. The speaker brief stated that the objective of the presentation was to discuss appropriate referral to the renal clinic, renal disease, complications and the management of patient care.

The Panel noted that the invitation described the meeting as an educational meeting for all health professionals where the speaker would discuss referrals to the renal clinic and management of kidney health and care.

The Panel noted that the Lilly speaker briefing referred to the presentation and the requirements of the Code. The briefing advised that it was the speaker's responsibility to ensure that the information in the slides was, *inter alia*, capable of substantiation and, in relation to non-Lilly products, fair, balanced, non-disparaging and consistent with the product label.

The Panel noted that the presentation entitled 'Referral: who, how, and if not, why not?', did not mention any specific medicine. A slide referring to quality outcome framework indicators referred to the percentage of patients with chronic kidney disease treated with an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB). From the slides it appeared that the presentation was about chronic kidney disease in general rather than that associated with diabetes and was consistent with the invitation in that regard.

The Panel noted that an email from the speaker submitted by Boehringer Ingelheim and Lilly stated *inter alia*, that his discussion of individual medicines or the management of diabetic renal disease. The speaker stated that on review of the slides none were promotional and no slides referred to diabetic renal disease or its management.

The Panel noted that the representative who was at the meeting had stated that questions were raised during the presentation on referrals to hospital but none were raised about Trajenta, either during or after the presentation, to the representative or the speaker.

The Panel noted that the parties' accounts differed. A decision had to be made on the evidence before it. A complainant had the burden of proving his/her complaint on the balance of probabilities. The Panel noted Boehringer Ingelheim and Lilly's submission and the accounts provided by the speaker and representative that there was no reference to Trajenta at the meeting. The complainant did not respond to a request to comment on the companies' response.

The Panel considered that the complainant had failed to establish that Trajenta was discussed at the meeting and consequently that any such discussion, including comparisons with other medicines within its class, was misleading and unbalanced as alleged. There was no evidence that any medicine had been disparaged as alleged. There was no evidence before the Panel to indicate that the meeting had promoted Trajenta and thus it was not disguised in that regard. No breaches of the Code were ruled.

A general practitioner complained about a local educational meeting jointly sponsored by Boehringer Ingelheim Limited and Eli Lilly & Company Limited to discuss referrals to the renal clinic and the management of kidney health and care. The meeting 'When to refer to the renal clinic' was held in April 2012. Boehringer Ingelheim and Lilly co-promoted Trajenta (linagliptin) for the treatment of type 2 diabetes.

COMPLAINT

The complainant stated that in his/her view the presentation, and in particular the speaker's comments on the management of diabetic complications, was overwhelmed by the unbalanced discussion and disguised promotion of Trajenta. For example, the speaker made unfettered reference to the key marketing messages for Trajenta, ie no modification of dosage necessary in diabetics with renal disease, that Trajenta represented an unmet need in such patients compared with other medicines in the same class, the inference that the other medicines in the class were suboptimal and represented an unacceptable safety profile and that Trajenta improved compliance by virtue of its single dosage strength. No counterpoints were offered in favour of the other medicines in the class.

When writing to Boehringer Ingelheim and Lilly the Authority asked the companies to respond in relation to the requirements of Clauses 7.2, 7.3, 8.1 and 12.1.

RESPONSE

Boehringer Ingelheim and Lilly had co-sponsored the non-promotional, educational meeting in question. The meeting was organised at the behest of a GP partner at the local health centre who had asked for an educational meeting to discuss the referral of patients with renal impairment from primary to secondary care.

The meeting was coordinated by a Lilly representative. The speaker, suggested by the GP, was considered an expert on this topic. The speaker agreed to be the sole speaker at the meeting. The Lilly representative made arrangements with the speaker that the meeting would be a non-promotional/educational event. The speaker created his own slide deck to discuss appropriate referrals to the renal clinic, renal diseases, complications and the management of patient care.

Lilly did not agree to the speaker's initial request to do the talk independently without paperwork and internal compliance procedures were duly followed and the meeting was documented. The speaker was briefed by the Lilly representative and the Lilly compliance administration team using a speaker briefing document (a copy was provided). No other materials were provided and the speaker prepared his own slides, which Lilly reviewed before the meeting. As per the speaker agreement, the slide review focused on fairness, balance, non-disparaging content, safety and consistency with the product label. As this was an educational meeting the review ensured that the slides contained no promotional content.

All meeting arrangements were finalised in accordance with Lilly standard operating procedures and the Code. The meeting invitation was approved and expressly referred to its educational nature, leaving the invitee in no doubt they would be attending an educational, non-promotional meeting. No promotional material was used or distributed during the meeting and as it was a non-promotional meeting no stand or promotional activity was permitted. The meeting was well attended.

Due to unforeseen circumstances the Lilly representative was unable to attend but arranged for a Boehringer Ingelheim representative to be there to ensure that the meeting ran smoothly. No other representative attended the meeting or was involved in any way.

The speaker's presentation, 'Referral: who, how, and if not, why not?' covered the meeting objectives referred to above and did not mention any treatment or products used in the management of type 2 diabetes including Trajenta. The Boehringer Ingelheim representative strongly refuted any suggestion that further discussion took place on any products including Trajenta. As no product discussions took place there was no scope for product comparisons. The companies noted that two attendees raised questions on the exact process of referring their patients to secondary care renal clinics, which further demonstrated the educational nature of the discussions at the meeting.

Based on the slide content, feedback from attendees and overall meeting arrangements, the companies were confident that this educational meeting was not in breach of Clauses 7.2, 7.3, 8.1, or 12.1.

In conclusion, Boehringer Ingelheim and Lilly noted the feedback from one of the attendees who stated that 'It's appreciated that Lilly will ask a consultant to speak covering our educational needs rather than a "promotional" talk'.

The companies submitted that the evidence outlined above demonstrated that they had complied with all requirements of the Code in terms of this educational meeting and therefore disputed the allegation that it constituted disguised promotion of Trajenta.

Following a request for further information, Boehringer Ingelheim and Lilly stated that they were fully committed to ensuring that all their activities were fully compliant with the Code and were disappointed that the complaint had been raised.

In relation to the phrase 'further discussions' at the meeting in question, the companies submitted that the meeting was entirely education and service related. There was no scope for product discussion at any point before, during, or after the meeting. The phrase, 'further discussions' was to emphasise clearly the educational purpose of this event. This was further evidenced by the statements from both the speaker and the Boerhinger Ingelheim representative, who were both clear in their recollection of the meeting as being fully non-promotional.

PANEL RULING

The Panel noted Boehringer Ingelheim and Lilly's submission that the meeting in question was organised at the behest of a GP partner who requested an educational meeting to discuss the referral of patients with renal impairment from primary to secondary care. The GP partner suggested the speaker as he was considered an expert on this topic. The meeting was coordinated

by a Lilly representative and the speaker had agreed to be the sole speaker at the meeting. A Boehringer Ingelheim representative had attended the meeting.

According to the companies the speaker had created his own slide deck with the objective of discussing appropriate referrals to the renal clinic, renal diseases, complications and the management of patient care. The Panel noted from the speaker/consultant agreement submitted by the companies that the title of the meeting was 'When to refer to the Renal Clinic'. The speaker brief stated that the objective of the presentation was for the speaker to discuss appropriate referral to the renal clinic and that the talk should discuss renal disease, complications and the management of patient care.

The Panel noted that the invitation to the meeting described it as an educational meeting for all health professionals where the speaker would discuss referrals to the renal clinic and management of kidney health and care.

The Panel noted that the Lilly speaker briefing referred to the presentation and the requirements of the Code, including Clauses 7.2 and 7.4. The briefing advised that it was the speaker's responsibility to ensure that the information in the slides was, *inter alia*, capable of substantiation and, in relation to non-Lilly products, fair, balanced, non-disparaging and consistent with the product label. There was no guidance about how the slides should be explained to the audience.

The Panel reviewed the presentation entitled 'Referral: who, how, and if not, why not?'. It provided a background to chronic kidney disease then discussed which patients should be seen in the renal clinic; the role of the renal clinic; reasons for referral; profiles for patients who should and should not be referred and advice on how to refer. There was no mention of any specific medicine. A slide referring to quality outcome framework indicators referred to the percentage of patients with chronic kidney disease treated with an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB). From the slides it appeared that the presentation was about chronic kidney disease in general rather than that associated with diabetes and was consistent with the invitation in that regard.

The Panel noted that an email from the speaker submitted by Boehringer Ingelheim and Lilly stated that he had no recollection of making any promotional comments during his talk which was very clearly on the referral of patients to the renal clinic. Discussion of individual medicines and the management of diabetic renal disease did not occur. The speaker stated that on review of the slides none were promotional and no slides referred to diabetic renal disease or its management. The speaker further stated that he knew nothing about Trajenta and had no practical or theoretical experience of its use. He had approached a GP in the practice where the meeting had been held who attended the meeting and who agreed that there was no promotional content nor were any promotional slides used. The speaker was disappointed that the complainant's concerns had not been raised directly.

The Panel noted that a statement from the representative who was present at the meeting stated that there were a number of questions raised during the presentation on referrals to hospital but no questions were raised about Trajenta, either during or after the presentation, to the representative or the speaker.

The Panel noted that the parties' accounts differed. A decision had to be made on the evidence before it. As stated in the Constitution and Procedure a complainant had the burden of proving his/her complaint on the balance of probabilities. The Panel noted Boehringer Ingelheim and Lilly's submission and the accounts provided by the speaker and representative that there was no reference to Trajenta at the meeting in question. The complainant was asked to comment on the companies' response to the complaint but did not respond.

The Panel considered that the complainant had failed to establish that Trajenta was discussed at the meeting and consequently that any such discussion, including comparisons with other medicines within its class, was misleading and unbalanced as alleged. No breach of Clauses 7.2 and 7.3 was ruled. There was no evidence that any medicine had been disparaged as alleged and thus no breach of Clause 8.1 was ruled. There was no evidence before the Panel to indicate that the meeting was promoting Trajenta and thus it was not disguised in that regard. No breach of Clause 12.1 was ruled.

Complaint received **25 June 2012**

Cases completed **14 September 2012**

MEMBER OF THE PUBLIC v MERCK SERONO

Alleged disclosure of patient data

A member of the public complained about an email from a market research agency, inviting her to take part in on online survey for Merck Serono about a new walking aid for patients with multiple sclerosis (MS). The complainant stated that the market research agency obtained her details from confidential information that she had given to Merck Serono two years previously when she had joined a patient support website for patients prescribed Merck Serono's MS medicine Rebif (interferon beta-1a).

The complainant noted the website had a specific web privacy promise that Merck Serono would not pass patient details onto a third party unless required to do so by law. In any event Merck Serono would need to ask for express permission as it was her personal medical data. Merck Serono claimed that the permission was not specific but was there and that the wording of the privacy policy just needed 'tightening up'.

The complainant was very concerned the market research agency claimed it was 'partnered' with several other medical market research agencies including one of the largest in the country, so she assumed that her details were now common property.

The complainant alleged that Merck seemed to think it had found a way to do market research on the cheap at the cost to patients of letting the world know that they had MS. This was deceitful and should be stopped as soon as possible.

The complainant had taken Rebif for six months until an adverse event. She was now on another medicine and was surprised and then dismayed to be contacted again.

The complainant had contacted Merck Serono and considered its response did not address the privacy issue or the continuation of the practice of sending patient data out for market research. The complainant noted that Merck Serono now intended to contact patients which seemed even more controversial.

The detailed response from Merck Serono is given below.

The Panel noted that the survey was sent to patients who had registered on a patient support website for Merck Serono's prescription medicine, Rebif. The Panel noted that the complaint was about provision of patients' email addresses by a pharmaceutical company to its market research agency and considered that the matter was potentially covered by the Code. The Code stated that pharmaceutical companies must comply with all applicable codes, laws and regulations to which they were subject. The Panel noted that the Data Protection Act 1998 was potentially relevant to matters within the scope of the Code and so in that regard the matter was covered by the Code.

The Panel noted that, in order to register on the website, the complainant had had to submit, *inter alia*, her email address and tick a box to declare that she had read and understood the privacy policy and website terms of use and give consent for her personal data to be processed in accordance with the privacy policy.

Point 1 of the privacy policy informed readers that Merck Serono might collect and process their personal data and might also ask the reader to complete surveys that Merck Serono used for research purposes although the reader did not have to respond to them. In the Panel's view it was thus clear that registered users might be contacted to complete a survey. Point 5 noted that information held might be used, *inter alia*, to carry out market research into medical conditions and the usefulness of the health information that Merck Serono provided. Point 6 stated that in specified circumstances Merck Serono might disclose personal information to third parties and, in addition, to any member of its group of companies. The Panel noted Merck Serono's submission that disclosure to a market research agency was not listed under Point 6 because, according to the Data Protection Act, the provision of personal data to third party data processors was not deemed to be the transfer of information which required the consent of the data subject. In the Panel's view, most readers of the privacy policy would not know the provisions for the Data Protection Act well enough to realize this.

The Panel considered that Merck Serono's privacy policy was not unacceptable. It was also not necessarily unacceptable for Merck Serono to have provided the complainant's email address to the market research agency in these circumstances. The market research agency had acted on behalf of Merck Serono and had been briefed to only use the email addresses for the purpose of the survey and to destroy any copy of the emails on completion of the survey.

Although the privacy policy could have been clearer that Merck Serono might use an agency to conduct market research, the emailed invitation from the agency clearly explained that it had been appointed by Merck Serono to carry out the survey. The email also informed the reader that their personal details would remain confidential and would not be passed on to anyone. Contact details were given for concerns or queries.

The Panel noted Merck Serono's submission that such research was always conducted by a market research agency to preserve the respondents' anonymity to Merck Serono and to ensure that the

research remained unbiased. The market research agency had confirmed that, subsequent to the dispatch of the email in question, all copies of the patients' email addresses were deleted or destroyed.

The Panel noted its comment above regarding the Data Protection Act and the application of the Code and that no evidence had been submitted to show that an appropriate judicial forum had formally considered this matter to be in breach of the Act. The Panel thus ruled no breach of the Code. The Panel did not consider that in the provision of the patients' email addresses to its agency, Merck Serono had failed to maintain high standards. The privacy policy applicable at the time made the position sufficiently clear. No breaches of the Code were ruled including Clause 2.

A member of the public complained about an unexpected email from a market research agency, inviting her to take part in on online survey for Merck Serono about a new walking aid for patients with multiple sclerosis (MS). The complainant stated that the market research agency had got her details from confidential information that she had given to Merck Serono two years previously when she had joined a patient support website for patients prescribed Merck Serono's medicine Rebif (interferon beta-1a). Rebif was indicated for the treatment of relapsing MS.

COMPLAINT

The complainant noted that on the website there was a specific web privacy promise that Merck Serono would not pass patient details onto a third party unless required to do so by law. The complainant questioned whether in any event Merck Serono would need to ask for express permission as it was her personal medical data.

The complainant had spoken to a senior director from Merck Serono UK who claimed that the permission was not specific but was there and that the wording of the privacy policy just needed 'tightening up'. The complainant emailed the German parent company but the enquiry was passed back to the UK. This had been going on since June.

The complainant posed the question of why this mattered as she did not have to take part in the survey.

The complainant submitted that the usual way to get patients' opinions was to ask for volunteers on patient support groups (most would not allow it), social media, patient forums or via online market research agencies. Getting a patient's contact details was key to this.

The complainant considered that there must be thousands of people on Rebif in the UK, most of whom would have joined the website to get support for using the medicine.

The complainant submitted that it got worse; the market research agency's website claimed it was 'partnered' with several other medical market research agencies including one of the largest in the country, so she assumed that her details were now common property.

The complainant alleged that Merck seemed to think it had found a way to do market research on the cheap at the cost to patients of letting the world know that they had MS. This was deceitful and should be stopped as soon as possible.

The complainant proposed to contact the main MS forums and warn people, knowing that journalists from national newspapers would pick it up, and had waited three weeks for the Medicines and Healthcare products Regulatory Agency (MHRA) to respond.

Following a request for further information from the case preparation manager, the complainant stated that she was on Rebif for six months until an adverse event which was reported by her consultant. She was now on another medicine and was surprised and then dismayed to be contacted again.

The complainant stated that letters from Merck Serono did not seem to address the privacy issue or the continuation of the practice of sending patient data out for market research (copies of the letters were provided). The complainant noted that Merck Serono now intended to contact patients which seemed even more controversial.

When writing to Merck Serono, the Authority asked it to consider the requirements of Clauses 1.8, 9.1 and 2 of the Code.

RESPONSE

Merck Serono confirmed that the complaint related to registration to its post-prescription patient support website which provided information to patients prescribed Rebif. Details of when the complainant registered to use the website were provided.

Merck Serono noted that the complainant was concerned that the personal details she submitted in order to access the website had been provided to a market research agency which then invited her to take part in an on-line survey. Merck Serono had commissioned the survey to evaluate a device which might help MS patients with mobility issues associated with foot drop, a recognised complication of MS.

Merck Serono stated that users undertook a formal registration process in order to access and use the website. The patient had to enter a code obtained from the patient support pack provided to them after being prescribed Rebif and then create a username (their email address) and a password to access the website. Access was only granted once all the required information had been completed and the patient had ticked a box to confirm that they had read and understood the terms of use and the privacy policy. The acceptance wording stated:

> 'I have read and understood the privacy policy and website terms of use, and I consent to be enrolled in the post prescription nursing support services, and for my personal data to be processed in accordance with the Privacy Policy.'

A link to the privacy policy and the terms of use was contained below this statement (a copy of the registration pages of the website and the terms of

use and the privacy policy (previous and current versions) were provided).

Merck Serono submitted that Point 1c of the privacy policy in its previous format stated:

> 'We may also ask you to complete surveys that we use for research purposes, although you do not have to respond to them.'

Point 5 of the privacy policy stated:

> 'We will not use your data for marketing purposes or for any purposes other than the specific purposes listed below.'

The purposes listed included the right:

> 'With your consent to carry out market research into medical conditions and the usefulness of the health information that we provide' (previous Point 5b).

Merck Serono submitted that the Data Protection Act 1998 stated that it must obtain consent of a data subject to use any personal data provided to it. It must also make it clear to the data subject as to how the personal data would be used. The privacy policy made it clear that data provided might be used to invite website users to participate in surveys and market research into medical conditions. Merck Serono was therefore confident that it had complied with the law in relation to the use of the complainant's personal data and thus did not consider it had breached Clause 1.8 of the Code.

Merck Serono noted that the complainant was also concerned that her data was provided to its market research agency, which then contacted her on behalf of Merck Serono to invite her to participate in the survey. The market research agency was engaged to carry out the survey on behalf of Merck Serono. The market research agency was provided with a list of email addresses of registered users of the website. No other details of registered users of the website were provided. The agency was under strict instructions not to use the data provided (email addresses) for any purpose other than to conduct the survey and it was asked to destroy the data provided upon completion of the survey. A copy of the instructions emailed to the market research agency was provided.

Merck Serono noted Point 6 of its privacy policy stated:

> 'We may disclose your personal information to third parties only in the following circumstances.'

The circumstances where it might disclose such information to a third party included a third party involved in any merger, acquisition or corporate restructuring of Merck Serono, adverse event reporting, enforcement of its terms of use, or to protect its rights or property or those of others.

Merck Serono submitted that the right to use a third party to assist with market research was not listed here because the Data Protection Act did not deem the provision of personal data to a third party data processor as a transfer of information which required the consent of the data subject. The Act stated that a data processor engaged to carry out services on another's behalf was not seen as a third party. A data processor (ie the market research agency) was defined by the Data Protection Act as 'any person (other than an employee of the data controller [ie Merck Serono]) who processes the data on behalf of the data controller'.

Merck Serono stated that for the purpose of processing of personal data, the Data Protection Act defined a third party as 'any person other than (a) the data subject [ie the website user], (b) the data controller, or (c) any data processor or other person authorised to process data for the data controller or processor [ie the market research company]'.

Merck Serono stated that in its view it had not contravened the Data Protection Act which governed the processing of personal data and thus had not breached Clauses 1.8, 9.1 or 2.

Merck Serono submitted that the invitation at issue was sent to registered users of the website on 11 June 2012. The email made it clear that the survey was commissioned by Merck Serono which had appointed the market research agency to carry out the survey on its behalf. Further, the email did not put any pressure or obligation on the recipient to respond to the survey and it indicated that the respondents' details would remain confidential and not be passed on to anyone. A copy of the email was provided.

Merck Serono noted that it obtained a very positive response to the survey; from 760 invitations it received 166 replies, 150 of which were received in the first week. The company did not receive any other negative feedback about the invitation to take part in the survey. Such research was always conducted by a market research agency in order to preserve the respondents' anonymity to Merck Serono and to ensure that the research remained unbiased and thus ensured high standards were kept.

Merck Serono submitted that it had not breached the terms of the Data Protection Act by engaging the market research agency to contact registered users to invite them to participate in the survey. The communication was consistent with the terms of the website privacy policy, and was certified in accordance with the requirements of the Code and Merck Serono thus denied any breach of Clauses 1.8, 9.1 and 2.

Whilst Merck Serono considered that it had acted entirely within the requirements of the law and the Code, it was, however, concerned to receive the complaint and had accordingly endeavoured to address the complainant's concerns. It had thus changed the website privacy policy to provide greater clarity as to its terms; in particular it had grouped Points 1c and 5b (as cited above). The new Point 5b read:

> 'We may use your data [...] to contact you, in the manner detailed below, to ask you to complete

surveys or to carry out market research into medical conditions and the usefulness of the health information that we provide, although you do not have to respond to them.'

The following provision had also been inserted:

'Market research/surveys – where we wish to conduct surveys or market research which we use for our own internal research purpose, we may engage an independent professional service provider for the sole purpose of conducting such survey or market research on our behalf. This is to preserve the anonymity of respondents and to ensure that the research is unbiased. In this event, we will contact you to obtain your consent prior to passing your details.'

Merck Serono submitted that if it undertook future market research/surveys with the website users, it would make the first contact rather than an independent professional service provider. This would include asking if the registered user would like to participate in the survey/market research and if so to ask him/her to confirm that he/she was happy for his/her details to be provided to an independent professional adviser who will contact him/her with regard to the survey/market research. A copy of the updated privacy policy was provided. Merck Serono submitted that the changes had been uploaded onto the website.

Merck Serono submitted that it had also reassured the complainant that the market research agency no longer held her details (or those of any other users) and that she would not be contacted again by Merck Serono or any third party data processing agent engaged by it to ask if she would like to participate in any survey or market research.

In Merck Serono's view it had endeavoured to address the complainant's concerns. It had responded swiftly to her, fully investigated her complaint and implemented actions to address her concerns. Copies of correspondence exchanged with the complainant were provided.

Merck Serono confirmed that only the complainant's email address was provided to the market research agency by Merck Serono as detailed above. Seven hundred and sixty (760) email addresses of registered users were provided to market research agency and the company instructed not to use them for any purpose other than to email the approved invitation; in particular the company must not pass the data to third parties and the data must be destroyed when the survey was complete. The market research agency had confirmed in writing that it had complied with Merck Serono's requirements (a copy was provided)

Merck Serono only used the market research agency to assist it with the survey. It used another agency to obtain feedback from registered users of the website in relation to the support information provided in February 2012.

Merck Serono stated that it had not been paid for the complainant's details. Merck Serono appointed the market research company to provide a service and paid it for the service provided.

Merck Serono concluded that by contacting the complainant to invite her to participate in the survey and passing her email address to a market research agency appointed by it for this sole purpose, it had not contravened the Data Protection Act or any other laws or regulations, and had therefore not breached Clause 1.8. The initial communication sent to respondents was consistent with the terms of the website privacy policy, complied with the Data Protection Act and was reviewed for compliance with the Code and certified accordingly. Furthermore Merck Serono had taken the complainant's concerns seriously and has acted to address them. Merck Serono considered that it had complied with the Code and in particular Clauses 1.8, 9.1 and 2.

PANEL RULING

The Panel noted that the Code applied to the promotion of medicines to members of the UK health professions and to appropriate administrative staff. It also applied to a number of areas which were non promotional, including information made available to the public about prescription only medicines. The Panel noted that the survey in question concerned a device. Whilst material or activities relating to devices generally fell outside the scope of the Code, the Panel noted that the survey was only sent to patients who had registered on a patient support website for Merck Serono's prescription medicine, Rebif. The Panel noted that the complaint before it was about provision of patients' email addresses by a pharmaceutical company to its market research agency and in that regard it considered that the matter was potentially covered by the Code. Clause 1.8 of the Code stated that pharmaceutical companies must comply with all applicable codes, laws and regulations to which they were subject. The Panel noted that in this case the provisions of the Data Protection Act 1998 were potentially relevant to matters within the scope of the Code and so in that regard the matter was covered by Clause 1.8. The Panel noted, however, that its ruling would be made according to the provisions of the Code; it could not make any decision with regard to adherence to the Data Protection Act.

The Panel noted that, in order to register on the website, the complainant had had to submit, *inter alia*, her email address and tick a box to declare that she had read and understood the privacy policy and website terms of use and give her consent for her personal data to be processed in accordance with the privacy policy.

Point 1 of the privacy policy informed readers that Merck Serono might collect and process their personal data and might also ask the reader to complete surveys that Merck Serono used for research purposes although the reader did not have to respond to them. In the Panel's view it was thus clear that registered users might be contacted to complete a survey. Point 5 noted that information held might be used, *inter alia*, to carry out market research into medical conditions and the usefulness

of the health information that Merck Serono provided. Point 6 of the privacy policy stated that in specified circumstances Merck Serono might disclose personal information to third parties and, in addition, to any member of its group of companies. The Panel noted Merck Serono's submission that disclosure to a market research agency was not listed under Point 6 because, according to the Data Protection Act, the provision of personal data to third party data processors was not deemed to be the transfer of information which required the consent of the data subject. In the Panel's view, most readers of the privacy policy would not know the provisions for the Data Protection Act well enough to realize this. The Panel noted that Merck Serono had since changed its privacy policy to include more explanation about the use of data for market research/surveys and its processes had also changed such that the first contact about market research/surveys would come from Merck Serono, not a third party agency.

The Panel considered that although Merck Serono had recently changed its privacy policy as a result of this complaint, its original privacy policy was not unacceptable. It was also not necessarily unacceptable for Merck Serono to have provided the complainant's email address to the market research agency in these circumstances. The market research agency had acted on behalf of Merck Serono and had been briefed to only use the email addresses for the purpose of the survey and to destroy any copy of the emails on completion of the survey.

Although the privacy policy could have been clearer that Merck Serono might use an agency to conduct market research, the emailed invitation from the agency clearly explained that it had been appointed by Merck Serono to carry out the survey. The email also informed the reader that their personal details would remain confidential and would not be passed on to anyone. Telephone and email contact details were given for readers with concerns or queries.

The Panel noted Merck Serono's submission that such research was always conducted by a market research agency to preserve the respondents' anonymity to Merck Serono and to ensure that the research remained unbiased. The market research agency had confirmed that, subsequent to the dispatch of the email in question, all copies of the patients' email addresses were deleted or destroyed.

The Panel noted its comment above regarding the Data Protection Act and the application of the Code and that no evidence had been submitted to show that an appropriate judicial forum had formally considered this matter to be in breach of the Act. The Panel thus ruled no breach of Clause 1.8. The Panel did not consider that in the provision of the patients' email addresses to its agency, Merck Serono had failed to maintain high standards. The privacy policy applicable at the time made the position sufficiently clear. No breach of Clause 9.1 was ruled.

The Panel noted its rulings above and ruled no breach of Clause 2.

Complaint received **4 July 2012**

Case completed **4 August 2012**

ANONYMOUS v TEVA

Venue for meeting

An anonymous, non-contactable complainant complained about a VAT management in practice meeting at a golf and country club where customers could enjoy a 'well maintained 9-hole golf course'. The meeting was sponsored by, *inter alia*, Teva.

The complainant alleged that this venue was in breach of the Code.

The detailed response from Teva is given below.

The Panel noted that the complainant was anonymous and non contactable. The complainant had the burden of proving their complaint on the balance of probabilities. The Code required that meetings be held at appropriate venues conducive to the main purpose of the event: lavish, extravagant or deluxe venues must not be used, companies must not sponsor or organize entertainment (such as sporting or leisure events) and companies should avoid using venues that were renowned for their entertainment facilities. The impression created by the arrangements must be borne in mind.

The Panel noted Teva's submission that delegates had no access to the golf course. The Panel considered that companies had to be mindful of the impression created by all of the arrangements for a meeting including the venue. A venue which described itself as a country club would have to be carefully checked to ensure that its facilities were appropriate bearing in mind the intended delegates, the nature of the meeting and the venue's reputation both locally and nationally. Teva had submitted that the venue in question was in no way renown for its entertainment facilities. There was no mention of the golf course on the meeting invitations. The Panel considered it would have been preferable if a venue without a small attached golf course had been chosen as such a facility might enhance the local profile of the venue. However on the particular circumstances of this case the Panel considered that the complainant had not established on the balance of probabilities that the venue was inappropriate in relation to the requirements of the Code and no breach was ruled accordingly.

An anonymous, non-contactable complainant alleged that a GP service provider was hosting a number of meetings over 2012 many of which he/she considered to be in breach of the Code. The Authority contacted the service provider which advised, *inter alia*, that Teva UK had agreed to support an event held in May at a country club hotel.

COMPLAINT

The complainant stated that the service provider had hosted its VAT management in practice meeting in May at a golf and country club where customers could enjoy a 'well maintained 9-hole golf course'.

The complainant alleged that this venue was in breach of Clause 19, specifically; 'the venue must be appropriate and conducive to the main purpose of the meeting; lavish, extravagant or deluxe venues must not be used; companies must not sponsor or organise entertainment (such as sporting or leisure events) and companies should avoid using venues renowned for their entertainment facilities'.

Teva was asked to respond in relation to Clause 19.1 of the Code.

RESPONSE

Teva submitted that the venue chosen for this financial management training workshop was entirely appropriate for such a meeting. Teva drew attention to the venue description available on various booking websites which described it as a small 3* hotel, conference and banqueting venue offering an excellent service for corporate or social guests alike. There was free car parking and free WiFi throughout the hotel. It was described as in a rural, tranquil setting but 8 minutes' drive from a main town with excellent roadways.

Teva submitted that the hotel was in no way renowned for its entertainment facilities. The presence of a 9-hole golf course (identified only on the hotel website and not in any material relating to the event), well maintained or otherwise, and a gym, was incidental to the provision of the meeting. Their presence alone did not constitute a lavish or extravagant venue which would be deemed inappropriate under the Code.

Teva confirmed that delegates (who were not customers of the hotel) had no access to, or benefit to access, the golf course as evidenced in a letter from the service provider. Teva pointed out that numerous venues used by the pharmaceutical industry, third party organisers and the NHS with comparable or higher quality facilities had been deemed suitable for such meetings in the past.

Teva submitted that the meeting in question concerned the management of VAT. There was no promotion by Teva, or any other party, of prescription only medicines.

By way of background, Teva explained that it contributed to the financing of such meetings as part of a corporate sponsorship package agreed annually with the service provider. The agreed funding supported marketing and educational events developed and executed by the service provider for its members. The events were organized and run by the service provider and Teva to date had no involvement in the content, venues or delegate invitations. They were arranged at suitable venues, taking into account factors such as proximity to delegates and travel times.

Teva submitted that the meeting in question was no exception, it was part of the service provider's educational programme and Teva's involvement was the provision of a corporate banner stand and the attendance by an account manager to facilitate Teva's corporate relationship with the service provider.

Teva provided a copy of the delegate list for the meeting which it submitted was targeted at primary care practice personnel interested in VAT management. This had been provided with the consent of the service provider, the meeting organisers.

Teva submitted that, in conclusion, should the Panel determine that this meeting fell within the remit of the Code, Teva would strongly argue that the venue used was not in breach of Clause 19.1 and was appropriate and conducive to the main purpose of the meeting.

PANEL RULING

The Panel noted Teva's submission that the events were organized and run by the service provider and Teva had no involvement in the content, venues or delegate invitations. It contributed to a corporate sponsorship package which supported marketing and educational events run by the service provider. The Panel did not accept Teva's inference that the meeting may not fall within the scope of the Code. Teva's funding was used specifically for, *inter alia*, educational events. Teva was therefore obliged to ensure that such events were appropriate meetings to sponsor in relation to the requirements of Clause 19.1 otherwise such sponsorship packages could be used by companies to circumvent the requirements of the Code. The Panel considered that the meeting fell within the scope of the Code.

The Panel noted that the complainant was anonymous and non contactable. The complainant had the burden of proving their complaint on the balance of probabilities.

Clause 19.1 required that meetings be held at appropriate venues conducive to the main purpose of the event. The relevant supplementary information gave more guidance: lavish, extravagant or deluxe venues must not be used, companies must not sponsor or organize entertainment (such as sporting or leisure events) and companies should avoid using venues that were renowned for their entertainment facilities. The impression created by the arrangements must be borne in mind.

The Panel noted that the one day course, attended by 18 delegates including practice managers, dispensing managers, finance administrators and one GP, examined VAT management and how it impacted on general practice. The Panel noted that Teva had submitted a letter from the service provider which explained that in general terms it chose venues that were centrally located to local general practices, had suitable event facilities and were cost efficient. Fixtures and access to sporting facilities were stringently checked. In this regard the Panel noted Teva's submission that in relation to the venue in question delegates were not customers of the hotel and therefore had no access to, or benefit to access, the golf course.

The Panel considered that companies had to be mindful of the impression created by all of the arrangements for a meeting including the venue. A venue such as the one at issue that described itself as a country club would have to be carefully checked to ensure that its facilities were appropriate bearing in mind the intended delegates, the nature of the meeting and the venue's reputation both locally and nationally. Teva had submitted that the venue in question was in no way renown for its entertainment facilities. There was no mention of the golf course on the invitations for the meeting in question. The Panel considered it would have been preferable if a venue without a small attached golf course had been chosen as such a facility might enhance the local profile of the venue. However, on the particular circumstances of this case the Panel considered that the complainant had not established, on the balance of probabilities, that the venue was inappropriate in relation to the requirements of Clause 19.1 and no breach of that clause was ruled accordingly.

During its consideration of this case the Panel was concerned to note that the invitation to the meeting did not bear a declaration of sponsorship as required by Clause 19.3 which required that such declarations should be sufficiently prominent such that readers were aware of them at the outset. The Panel asked that Teva be made aware of its views in this regard.

Complaint received **6 July 2012**

Case completed **1 August 2012**

CASE AUTH/2526/8/12

DOCTOR v SANOFI PASTEUR MSD

Shingles awareness campaign

A doctor alleged that an advertisement placed by Sanofi Pasteur MSD in a lifestyle magazine was in breach of the Code.

The advertisement, which was presented in the style of an advertorial, had a 'Shingles Aware' logo in the top left-hand corner. The headline read 'If, like 90% of UK adults, you have ever had chickenpox, there is a 1 in 4 chance you will develop shingles at some point in your lifetime'. The following three paragraphs described the symptoms of shingles and advised the reader about the need to see a GP as soon as possible. Following these paragraphs were the separate statements, in a bolder font, 'It is possible to prevent shingles' and 'See your GP who can give you more information'. Readers were then directed to other information on the shingles aware website (sponsored by Sanofi Pasteur MSD) or an independent patient organization website. Readers could scan a QR Code with a smart phone to access the shingles aware website.

Sanofi Pasteur MSD had recently launched Zostavax (shingles (herpes zoster) vaccine (live)) for the immunization of the over 50s to prevent herpes zoster (shingles) and herpes zoster-related post-herpetic neuralgia.

The detailed response from Sanofi Pasteur MSD is given below.

The Panel noted that Zostavax was the only medicine for the prevention of shingles.

The Panel noted that the headline stated that 90% of UK adults had a 1 in 4 chance of developing shingles. The following three paragraphs informed the reader that shingles occurred more frequently in those aged 50 years or more and then described the symptoms of shingles. Although the reader was told that symptoms were 'usually mild', they could be 'very unpleasant for some'. Further details were provided.

The Panel noted that following the paragraphs which described the symptoms of shingles, the statement 'It is possible to prevent shingles' appeared in bolder, darker and thus more prominent font. This statement was clearly separated from the previous text and in that regard the Panel considered that the reader's eye would be drawn to it. This statement was followed by a separate equally prominent statement 'See your GP who can give you more information'. The prominence, font colour and position of the statement was such that some readers would associate it particularly with the preceding statement and conclude that their GP could provide more information particularly on the prevention of shingles. The Panel's view was that the final 'take home' message from the advertisement was one of prevention.

The Panel noted that whilst disease awareness was in principle a legitimate and helpful activity, caution should be exercised when there was only one product available. Whilst the advertisement discussed symptoms and some relatively rare but serious consequences of shingles, there was very little discussion of treatment. The emphasis was on prevention. The Panel queried whether it was sufficiently balanced in this regard given the need to exercise caution.

The Panel considered that companies that published website addresses as an integral part of 'the message' of their material as in the present case, and directed the public to seek further information about that message from such sites needed to be satisfied that the website content was reasonable as far as the Code was concerned. This was so whether or not they had any input to, or ability to, influence the content. If this were not the case then companies could refer to independent sites as a means of circumventing the Code.

Readers were directed to two websites; the company-sponsored shingles aware website and an independent patient organization website. On the homepage of the shingles aware website was a Sanofi Pasteur MSD website and on the home page there were two separate buttons; one marked 'Information for the public' and the other marked 'Information for healthcare professionals'. Below the 'Information for the public' button was the statement 'If you want further advice on shingles vaccination, please speak to a healthcare professional'. The Panel queried whether it was appropriate to highlight shingles vaccination and encourage members of the public to seek such advice on the homepage, given the need to exercise caution. It might also encourage members of the public to access the health professional material to seek further information about vaccination. On the introductory page to the public section of the website there was also a button marked 'Can shingles be prevented?'. By clicking on that button, readers were told that 'It is possible to prevent shingles. See your GP or other healthcare professionals who can give you more information'.

The first feature on the homepage of the patient organization website was the news item: 'A vaccine for the prevention of shingles is now available. Adults aged 50 and over will be able to have the shingles vaccine (know as Zostavax) through their NHS GP, pharmacist or private healthcare provider'. Readers were told that any registered doctor who believed that the vaccine would benefit a patient was able to prescribe and administer it. The results of two clinical trials were briefly detailed.

In the Panel's view, having read about the possible symptoms and long term effects of shingles, readers

would be keen to avoid developing the disease and to seek ways in which to prevent it. Readers were told that prevention was possible and directed, *inter alia*, to a website which, at the outset, highlighted the availability of Zostavax. The Panel noted its comments above about the emphasis given to prevention in the advertisement, and its view that the website addresses were an integral part of the advertisement and the company's responsibility in that regard. The Panel considered that the advertisement posed the question 'how do you prevent shingles?' and answered that question with the name of the product which was the subject of the first item on the homepage of the patient organisation website. The Panel considered that the combined effect of the advertisement and websites was to promote Zostavax to the general public. A breach of the Code was ruled.

The Panel considered that the material (the advertisement and websites combined) was not balanced. There was a disproportionate emphasis on vaccination, including the name of the vaccine. A breach of the Code was ruled.

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

The Panel did not consider that a ruling of a breach of Clause 2 was warranted. A ruling of a breach of that clause was regarded as a sign of particular censure and reserved for such. The Panel was concerned about the material. Nonetheless, taking all the circumstances into account it considered that its ruling of a breach of the Code above, in that high standards had not been maintained, provided adequate censure and, on balance, ruled no breach of Clause 2.

A doctor complained about an advertisement (ref UK15219n 04/12) placed by Sanofi Pasteur MSD Ltd in City Life Cardiff, Summer 2012.

The advertisement, which was presented in the style of an advertorial, had a 'Shingles Aware' logo in the top left-hand corner. The headline read 'If, like 90% of UK adults, you have ever had chickenpox, there is a 1 in 4 chance you will develop shingles at some point in your lifetime'. The following three paragraphs described the symptoms of shingles and advised the reader about the need to see a GP as soon as possible. Following these paragraphs were the separate statements, in a bolder font, 'It is possible to prevent shingles' and 'See your GP who can give you more information'. Readers were then directed to other information on the shingles aware website (sponsored by Sanofi Pasteur MSD) or an independent patient organization website. Readers could scan a QR Code with a smart phone to access the shingles aware website.

Sanofi Pasteur MSD marketed Zostavax (shingles (herpes zoster) vaccine (live)) indicated for the immunization of the over 50s to prevent herpes zoster (shingles) and herpes zoster-related post-herpetic neuralgia.

COMPLAINT

The complainant was concerned that the advertisement breached the Code.

When writing to Sanofi Pasteur MSD the Authority asked it to consider Clauses 2, 9.1, 22.1 and 22.2 of the Code.

RESPONSE

Sanofi Pasteur MSD stated that shingles (also known as herpes zoster) was a potentially serious condition that could lead to long-term, debilitating complications, such as post-herpetic neuralgia (PHN), which adversely affected patients' quality of daily life. Shingles was caused by reactivation of the varicella zoster virus (VZV), which remained latent after primary infection, ie chickenpox. Although there were many reasons for reactivation, a decline in VZV-specific cell mediated immunity, most commonly due to ageing, was thought to play a major role.

Over 90% of adults raised in the UK were seropositive for VZV and therefore at risk of developing shingles (Department of Health, 2011).

The estimated annual number of herpes zoster cases in England and Wales in the immunocompetent population of 60 years and older was 88,650 (95% credibility intervals 65,000–113,000), of which 18,200 (13,500–23,300) were estimated to remain in pain after 3 months. There were an estimated 1,750 (1,300–2,200) hospitalisations in the 60 plus age group every year, and it was estimated that 55 (54-56) people died with zoster recorded as a cause of death.

Currently herpes zoster and its complications was managed symptomatically and treatment did not address the underlying pathology leading to a clear unmet need in the patient population.

Antiviral therapy was the standard treatment for herpes zoster and shortened the duration of acute herpes zoster. However, there was little evidence to show that it was effective if given more than 72 hours after the onset of the rash. Furthermore, antivirals did not prevent the development of PHN.

PHN was non-resolving and there were no curative therapies. Despite extensive research and development, the analgesics used to treat PHN were not very effective and at best afforded around 50% pain relief for only half of patients treated (Hempenstall *et al*, 2005; Scott *et al* 2003). There was a lack of data on the co-morbidities resulting from pain. People with PHN also suffered from moderate to severe depression and other related co-morbidities affected their quality of life and activities of daily living (Bouhassira *et al*, 2011; Oster *et al*, 2005; van Seventer *et al*, 2006). Lack of sleep was another co-morbidity. PHN occurred predominantly in the elderly (mean age 75 years old) and could therefore tip people into dependency.

Market research conducted on behalf of Sanofi Pasteur MSD in July 2011 to assess patients' understanding of shingles and its sequelae involved a nationally representative selection of UK adults aged 50-79 years. Almost all respondents were aware of shingles, however it was clear from the research that there was a low understanding of the details and a misunderstanding of the severity of the disease, for

example only 10% were aware of PHN. Of particular note was the finding that those individuals who had direct or indirect experience of shingles assigned a much higher severity score to the condition than those who had no experience of the disease. This research indicated an urgent need for disease awareness education in the 50 plus age group who were at particular risk for shingles and its consequences.

The potential seriousness of shingles and its commonest complication of PHN had been recognised by the Joint Committee on Vaccination and Immunisation (JCVI) – a Standing Advisory Committee with the purpose 'To advise the Secretary of State for Health and Welsh Ministers on matters relating to the provision of vaccination and immunisation services, being facilities for the prevention of illness'.

On 29 March 2010, the JCVI issued the following statement on herpes zoster vaccine:

> 'JCVI reviewed medical, epidemiological, and economic evidence as well as vaccine safety and efficacy data relevant to a herpes zoster (shingles) vaccination programme. Based on the evidence, a universal herpes zoster vaccination programme for adults aged 70 years up to and including 79 years is recommended provided that a licensed vaccine is available at a cost effective price.'

Based on this recommendation and the availability of a vaccine, the Department of Health issued a tender for the shingles vaccine with the aim of commencing a vaccination programme for those aged 70-79 years in 2013.

Sanofi Pasteur MSD contended therefore that, given the significant burden imposed by shingles, a disease awareness campaign benefitted patients and the wider healthcare environment.

Sanofi Pasteur MSD was aware that the Code set standards for the professional, ethical and transparent advertising and promotion of medicines for prescribing to health professionals to ensure the appropriate use of medicines and support the provision of high quality healthcare. With this in mind, it devised a disease awareness programme on shingles and PHN following the JCVI recommendation for a shingles vaccination programme, to coincide with the launch of Zostavax. To underpin this campaign, Sanofi Pasteur MSD used evidence from clinical trials, databases (GPRD) and market research.

Sanofi Pasteur MSD also undertook a due diligence process as it was the only manufacturer of a shingles vaccine. It liaised with the Medicines and Healthcare products Regulatory Agency (MHRA) over promotional materials as well as having many of these materials pre-vetted by the MHRA. Sanofi Pasteur MSD noted the MHRA guidance on disease awareness campaigns which stated that the primary purpose of such a campaign must be to increase the awareness of a disease and to provide health educational information on that disease and its management. It should not promote the use of a particular medicine or medicines. It further stated that the emphasis should be on the condition and its recognition rather than on treatment options. Sanofi Pasteur MSD submitted that the shingles disease awareness campaign had been pre-vetted by the MHRA and changed on the MHRA's recommendation. This pre-vetting demonstrated that the campaign was compliant with the MHRA disease awareness campaign guidelines. The campaign materials emphasised more the importance of disease recognition, the signs and symptoms of the disease, that the disease was usually mild and resolved without sequelae with prompt treatment, the possible complications and finally mentioning the possibility of prevention without actually stating that there was a vaccine to prevent shingles. Sanofi Pasteur MSD submitted that the disease awareness campaign was fair and balanced.

The advertisement for shingles that was placed in magazines appealed to readers aged 50 years and over, at particular risk of shingles and therefore in need of education on this disease, was written in a style that a lay-person could understand; it avoided medical terminology and provided a clear description of symptoms and the need to seek medical attention urgently if shingles was suspected. There was a simple explanation of the connection between an earlier episode of chickenpox and a later episode of shingles to ensure that the reader recognised that they might be at risk of shingles; this was important as although the market research indicated that many adults associated shingles with chickenpox, there was not universal recognition of this connection. Great care was taken to ensure the facts were not over-exaggerated and that the advertisement would raise awareness of shingles and prompt patients to seek treatment if they developed shingles. The advertisement stated that the symptoms of shingles were usually mild, most people recovered, shingles varied in its presentation, patients should see their GP within 72 hours of the rash occurring, most people did not have any long term effects but serious complications of the eye could occur if shingles developed in the eye. As this was a disease awareness campaign Sanofi Pasteur MSD added a short statement that it was possible to prevent shingles – but did not mention a product.

To further balance the information in the advertisement, Sanofi Pasteur MSD also included the name of a patient support website which could provide further independent information.

Sanofi Pasteur MSD submitted that the information contained in this advertisement formed part of a disease awareness campaign for the public. The aim of the campaign was to provide general information on shingles, the range of presenting symptoms and sequalae related to the disease. In particular, the campaign focused on the need for patients to seek treatment promptly. The description of shingles symptomology emphasised that the acute symptoms of shingles were usually mild and that most people recovered without sequelae.

However, it was important for the public to appreciate that shingles varied in its presentation from person to person both in its acute presentation and also in longer term consequences. It was important for patients with shingles to see their GP within 72 hours of the rash occurring in order to assess the need for antiviral therapy which might inhibit replication of VZV, thereby reducing the duration of viral shedding, increasing rash healing and reducing the severity and duration of pain (Johnson and Dworkin, 2003). There was little evidence to show that antiviral therapy was effective if given more than 72 hours after the onset of the rash. Shingles affecting the eye region (ophthalmic shingles) occurred in 10-20% of shingles patients (Cunningham *et al*, 2008). Without antiviral therapy, 50%-72% of patients with periocular herpes zoster would have involvement of the ocular structures and develop chronic disease; in one study, 20% of patients with herpes zoster uveitis were found to be legally blind in the involved eye (Dworkin *et al*, 2007).

The layout with the image of a woman, with the barbed wire belt representing the pain of shingles, holding a photograph with her younger self suffering from chickenpox, was designed to provide a simple link between childhood chickenpox and later reactivation of the virus leading to shingles. This striking image aimed to trigger a recognition that anyone who had suffered from chickenpox might be at risk of shingles and therefore should be aware of the need to seek urgent medical attention should symptoms arise.

Sanofi Pasteur MSD stated that because of the range of severity of symptoms, the advertisement was careful not to exaggerate the symptoms experienced by most people with shingles; 'the symptoms of shingles are usually mild but can be very unpleasant for some'. PHN was described as part of the spectrum of complications but it was made clear that most people recovered without sequelae.

The MHRA guidance stated that an important aspect of any health promotion campaign was to raise awareness of the symptoms so that members of the public could seek early diagnosis and treatment, minimise disease progression or avoid complications. The shingles campaign aimed to raise awareness of the need for medical attention within 72 hours of appearance of the rash in order that the GP could assess the need for antiviral treatment. This timing was critical as there was little evidence to show that antiviral therapy was effective if given more than 72 hours after the onset of the rash.

Sanofi Pasteur MSD submitted that a vaccine was available indicated for the prevention of herpes zoster and post-herpetic neuralgia in individuals aged 50 years and over. A discussion of shingles in the 50 plus age group would not be complete or balanced without an indication that a means of prevention was available. Prevention was mentioned within the context of disease awareness because there was a vaccine indicated for the prevention of herpes zoster and PHN in individuals aged 50 years and over (Zostavax). This indication was put into the context of disease management and formed a minor part of the disease awareness messages. There was no mention of vaccination and neither the brand name nor the generic name of the vaccine were included in the advertisement. Sanofi Pasteur MSD asserted, therefore, that the advertisement was not in breach of Clause 22.2. It was part of a *bona fide* disease awareness campaign as described in the supplementary information to Clause 22.2. Sanofi Pasteur MSD had taken care to ensure that the disease information provided in the advertisement was fair and balanced. There was no mention of specific products, thus there were no statements made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine. Sanofi Pasteur MSD asserted it had also complied with the MHRA's guidance on disease awareness campaigns in that the primary purpose of its campaign was to increase awareness of shingles and to provide information on shingles and its management and that it did not promote the use of a particular medicine. Sanofi Pasteur MSD worked closely with the MHRA to ensure this fair balance.

Sanofi Pasteur MSD submitted that the need to obtain medical attention was not accompanied by any recommendations for treatment as these would be determined by the GP according to individual patient need. There was no mention of vaccination and neither the brand name nor the generic name of the vaccine were contained in the advertisement.

Sanofi Pasteur MSD submitted that it always strove to maintain the highest standards in all its activities. It was the only manufacturer of a vaccine licensed to prevent shingles. As such it recognised that it had an onus in its disease awareness campaign to focus on disease education and provide details of where to get appropriate advice. The company submitted that the advertisement in question fulfilled this in a fair and balanced manner. The advertisement raised the awareness of shingles as a potentially serious disease but stated that most cases were mild and recover, that the presentation of shingles was variable and so some patients might need treatment – treatment was not specified as the patient consultation with the GP would decide appropriate treatment which might include options apart from medicines, that patients should see their GP within 72 hours of a rash appearing, that most people did not have any long term effects and warned that if shingles affected the eye serious complications of the eye could occur. The advertisement also stated that it was possible to prevent shingles and that the patient should contact their GP for more information.

Hence in maintaining high standards, Sanofi Pasteur MSD considered that the information was accurate, up-to-date, capable of substantiation, comprehensive, balanced, fair and readable.

Sanofi Pasteur MSD stated that it had not prejudiced patient safety and/or public health. There had been no inducements to prescribe. No product had been mentioned in the advertisement. As part of the disease awareness campaign prevention had had only one mention and Sanofi Pasteur MSD asserted that this was entirely reasonable given that the vast majority of content related to disease and treatment.

In summary, Sanofi Pasteur MSD asserted that, given the significant burden imposed by shingles, a disease awareness campaign was of benefit to patients and the wider healthcare environment. Sanofi Pasteur MSD also believed this disease awareness campaign was fair and balanced.

Sanofi Pasteur MSD asserted that the advertisement was not in breach of Clause 22.2 of the Code. It formed part of a *bona fide* disease awareness campaign as described in the supplementary information to Clause 22.2.

Sanofi Pasteur MSD had taken care to ensure that the disease information provided in the advertisement was fair and balanced. Sanofi Pasteur MSD therefore considered that the advertisement formed part of a *bona fide* disease awareness campaign and did not constitute an advertisement of a prescription only medicine to the public and was not in breach of Clause 22.1.

Sanofi Pasteur MSD also considered that the information was accurate, up-to-date, capable of substantiation, comprehensive, balanced and fair, high standards had been maintained and there was therefore no breach of Clause 9.1.

Sanofi Pasteur MSD stated that this advertisement had not prejudiced patient safety and/or public health. Taking into account Sanofi Pasteur MSD's reasoning for its shingles disease awareness campaign and its justification for the advertisement in question, Sanofi Pasteur MSD therefore submitted that there had been no breach of Clause 2.

PANEL RULING

The Panel noted that the supplementary information to Clause 22.2, Information to the Public, stated that a company could conduct a disease awareness campaign provided that the purpose was to encourage the public to seek treatment for symptoms while in no way promoting the use of a specific medicine. It was stated that particular care must be taken where the company's product, even though not named, was the only medicine relevant to the disease or symptoms.

The Panel noted that with regard to the shingles awareness campaign, Zostavax, a vaccine recently launched by Sanofi Pasteur MSD, was the only medicine for the prevention of shingles. The vaccine was only for use in patients aged 50 years or more.

The Panel noted that the headline to the advertisement in question told the reader that 90% of UK adults had a 1 in 4 chance of developing shingles. The following three paragraphs of text informed the reader that shingles occurred more frequently in those aged 50 years or more and then went on to describe the symptoms of shingles. Although the reader was told that symptoms were 'usually mild', they could be 'very unpleasant for some'. The pain associated with shingles was described as 'burning' and might be 'extreme' and that after 'painful blisters burst' and crusted over some people would continue to feel 'extreme pain' that could continue for 'many months' or 'even years'. Readers were further told that this pain could 'prevent sufferers from living a normal life' and that the lightest touch to the skin could be 'painful and distressing'. Shingles varied from person to person and some people would require treatment. Readers were advised to seek medical help within 72 hours of developing a rash and that if shingles developed in the eye it could lead to 'decreased vision or even permanent blindness'.

The Panel noted that following the paragraphs which described the symptoms of shingles, the statement 'It is possible to prevent shingles' appeared in bolder, darker and thus more prominent font. This statement was clearly separated from the previous text and in that regard the Panel considered that the reader's eye would be drawn to it. This statement was followed by a separate equally prominent statement 'See your GP who can give you more information'. The prominence, font colour and position of the statement was such that some readers would associate it particularly with the preceding statement and conclude that their GP could provide more information particularly on the prevention of shingles. The Panel's view was that the final 'take home' message from the advertisement was one of prevention.

The Panel noted that whilst disease awareness was in principle a legitimate and helpful activity, caution should be exercised when there was only one product available. Whilst the advertisement discussed symptoms and some relatively rare but serious consequences of shingles, there was very little discussion of treatment. The emphasis, as described above, was on prevention. The Panel queried whether it was sufficiently balanced in this regard given the need to exercise caution.

The Panel noted that the supplementary information to Clause 24.6, Sites Linked via Company Sites, stated that such sites were not necessarily covered by the Code. The Panel noted that Clause 24.6 applied to links from a company website (rather than hard copy material) to another site and thus was not directly applicable to the circumstances of this case. Nonetheless, the Panel noted that whether a linked site came within the scope of the Code had to be decided on a case by case basis. The Panel considered that companies that published website addresses as an integral part of 'the message' of their material as in the present case, and directed the public to seek further information about that message from such sites needed to be satisfied that the website content was reasonable as far as the Code was concerned. This was so whether or not they had any input to, or ability to, influence the content. If this were not the case then companies would be able to refer to independent sites as a means of circumventing the Code.

Readers were directed to two websites; the company-sponsored shingles aware website and an independent patient organization website. On the home page of the shingles aware website there were two separate buttons; one marked 'Information for the public' and the other marked 'Information for healthcare professionals'. Below the 'Information for

the public' button was the statement 'If you want further advice on shingles vaccination, please speak to a healthcare professional'. The Panel queried whether it was appropriate to highlight shingles vaccination and encourage members of the public to seek such advice on the homepage, given the need to exercise caution. It might also encourage members of the public to access the health professional material to seek further information about vaccination. On the introductory page to the public section of the website there was also a button marked 'Can shingles be prevented?'. By clicking on that button, readers were told that 'It is possible to prevent shingles. See your GP or other healthcare professionals who can give you more information'.

The first feature on the home page of a patient organization website was the following news item: 'A vaccine for the prevention of shingles is now available. Adults aged 50 and over will be able to have the shingles vaccine (know as Zostavax) through their NHS GP, pharmacist or private healthcare provider'. Readers were told that any registered doctor who believed that the vaccine would benefit a patient was able to prescribe and administer it. The results of two clinical trials were briefly detailed.

In the Panel's view, having read about the possible symptoms and long term effects of shingles, readers would be keen to avoid developing the disease and to seek ways in which to prevent it. Readers were told that prevention was possible and directed, *inter alia*, to a website which, at the outset, highlighted the availability of Zostavax. The Panel noted its comments above about the emphasis given to prevention in the advertisement, and its view that the website addresses were an integral part of the advertisement and the company's responsibility in that regard. The Panel considered that the advertisement posed the question 'how do you prevent shingles?' and answered that question with the name of the product which was the subject of the first item on the homepage of the patient organisation website. The Panel considered that the combined effect of the advertisement and websites was to promote Zostavax to the general public. A breach of Clause 22.1 was ruled.

The Panel considered that the material (the advertisement and websites combined) was not balanced. There was a disproportionate emphasis on vaccination, including the name of the vaccine, such that the caution urged by the relevant supplementary information to Clause 22.2 had not been exercised. The Panel noted its ruling of a breach of Clause 22.1 above and ruled a breach of Clause 22.2.

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

The Panel did not consider that a ruling of a breach of Clause 2 was warranted. A ruling of a breach of that clause was regarded as a sign of particular censure and reserved for such. The Panel was concerned about the material. Nonetheless, taking all the circumstances into account it considered that the ruling of a breach of Clause 9.1 provided adequate censure and, on balance, ruled no breach of Clause 2.

Complaint received **25 July 2012**

Case completed **28 September 2012**

CODE OF PRACTICE REVIEW – November 2012

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

2474/1/12	**Employee v GlaxoSmithKline**	**Promotional activities and training**	**Breaches Clauses 3.2, 9.1 and 15.2**	**No appeal**	**Page 3**
2496/4/12	**Allergan/Director v Merz**	**Promotion of Xeomin and Bocouture and breach of undertaking**	**Breach Clause 2** **Three breaches Clause 7.2** **Two Breaches Clause 7.3** **Two Breaches Clause 7.4** **Breach Clause 9.1** **Two Breaches Clause 25**	**Appeal by complainant**	**Page 18**
2501/4/12	ALK-Abelló v Meda	Promotion of EpiPen	No breach	No appeal	Page 30
2504/5/12	Anonymous ex-employee v Sanofi	Activities of sales and medical teams	No breach	No appeal	Page 33
2506/5/12 and 2507/5/12	**AstraZeneca v Lilly and Daiichi-Sankyo**	**Efient leavepiece**	**Breach Clause 2** **Four breaches Clause 3.2** **Six breaches Clause 7.2** **Two breaches Clause 7.9** **Two breaches Clause 9.1**	**No appeal**	**Page 37**
2514/6/12	**Voluntary admission by Baxter**	**Failure to certify an advertisement**	**Breaches Clauses 9.1 and 14.1**	**No appeal**	**Page 45**
2516/6/12	**Allergan/Director v Merz**	**Breach of undertaking**	**Breaches Clauses 2, 9.1 and 25**	**No appeal**	**Page 47**
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2523/7/12	Anonymous v Teva	Venue for meeting	No breach	No appeal	Page 70
2526/8/12	**Doctor v Sanofi Pasteur MSD**	**Shingles awareness campaign**	**Breaches Clauses 9.1, 22.1 and 22.2**	**No appeal**	**Page 72**

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

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.