NUMBER 84 May 2014

CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

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

COMPLAINTS AND NUMBER OF CASES TO BE CONSIDERED IN 2013 UP ON 2012

In 2013 the PMCPA received 80 complaints compared with 78 in 2012. There were 84 complaints in 2011, 86 complaints in 2010, 92 complaints in 2009 and 112 in 2008.

There were 105 cases to be considered in 2013, compared with 84 in 2012. The number of cases usually differs from the number of complaints because some complaints involve more than one company and others for a variety of reasons do not become cases at all.

The number of complaints from health professionals in 2013 (16) was just one more than the number from pharmaceutical companies (both members and non-members of the ABPI) (15). In addition there were 10 complaints from anonymous health professionals. The more complex cases considered by the Authority are generally inter-company complaints which often raise a number of issues.

There were three complaints were made by members of the public and six by employees/ex-employees.

There were 13 other anonymous complaints in addition to the ten from anonymous health professionals. One was from an anonymous employee.

In addition there was one complaint from the MHRA, one from a journalist and one from a publisher.

The remaining 14 complaints were nominally made by the Director and arose from voluntary admissions by companies and alleged breaches of undertakings.

TIME TO SIT AND PASS APPROPRIATE REPRESENTATIVES EXAMINATION

Clause 16.3 of the Code requires representatives to take an appropriate examination within their first year of employment as a representative and pass it within two years of starting such employment. The Director of the PMCPA may agree to extend the one or two year time periods if extenuating circumstances have prevented the representative complying with the time limits.

It is sometimes the case that when a representative applies for an extension, they calculate the one or two year limit from the date they first went out on territory – which in some cases can be 6-7 weeks after they were first employed.

Companies are reminded that the 'examination clock' starts to tick from the day an individual is first employed as a representative, not from the first day they go out on territory.

NEW INDEPENDENT MEMBERS OF THE APPEAL BOARD

Mr Christopher Goard, Mr David Mills and Dr John Watkins have recently been appointed to the Code of Practice Appeal Board as independent members. All are welcomed by the Authority. Mr Goard joins as the member representing patients' interests. Mr Mills joins as an independent pharmacist. Dr Watkins joins as an independent medical member.

MHRA ANNUAL MEETING AND REPORT

The Advertising Standards Unit of the Medicines and Healthcare Products Regulatory Agency has published its annual report for 2013 (available from www.mhra.gov.uk).

Although the report showed, in the section on complaints by category of medicine, an increase in the number of cases upheld in the prescription sector (from 4 in 2012 to 10 in 2013) this was largely due to recent scrutiny of abbreviated advertisements following changes in UK law and consequential changes to the Code. These cases aside, the overall downward trend in the number of advertising cases in the prescription sector continued in 2013. The MHRA remains supportive of self-regulation.

CODE OF PRACTICE TRAINING

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

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

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

Friday 26 September 2014

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

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

HOW TO CONTACT THE AUTHORITY

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

www.pmcpa.org.uk

Telephone: 020 7747 8880
Facsimile: 020 7747 8881

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or 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
Tannyth Cox: 020 7747 8883

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

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

REMINDER ABOUT THE ABPI UNACCREDITED EXAMINATION

Companies are reminded that the ABPI unaccredited examination will not be offered after 31 December 2015. Those relying on completing this examination should ensure that bookings are made in good time as it is likely that there will be less sittings for this examination as demand declines. Further details can be found at www.abpi.org.uk.

PUBLISHED REVIEW – ETHICAL PHARMACEUTICAL PROMOTION AND COMMUNICATIONS WORLDWIDE: CODES AND REGULATIONS

A review has been recently published (Francer *et al*, Philosophy, Ethics and Humanities in Medicine, 2014) that discusses codes of practice and self-regulation around the world. Heather Simmonds, Director of the PMCPA was one of the authors of the review which was written as part of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA's) Code Compliance Network activities. Copies of the paper can be found at http://www.peh-med.com/content/9/1/7.

PHARMACISTS REGISTERED IN THE UK ACTING AS FINAL SIGNATORIES

The 2014 Code of Practice for the Pharmaceutical Industry allows pharmacists registered in the UK to certify materials referred to in Clause 14.3; such materials previously had to be certified by a registered medical practitioner.

Clause 14.1 requires that promotional material must not be issued unless its final form, to which no subsequent amendments will be made, has been certified by two persons on behalf of the company in the manner provided for by this clause. One of the two persons must be a registered medical practitioner or a pharmacist registered in the UK or, in the case of a product for dental use only, a registered medical practitioner or a pharmacist registered in the UK or a UK registered dentist.

The material listed in Clause 14.3 must be certified in a manner similar to that provided for by Clause 14.1.

In accordance with Clause 14.4, companies are required to provide names and qualifications of their nominated signatories to the PMCPA (and also to the Medicines and Healthcare Products Regulatory Agency (MHRA)). When notifying the PMCPA it would be helpful to provide in addition the registration status of those listed with either pharmacy degrees or membership of the Royal Pharmaceutical Society. Companies are reminded that anyone referred to as a UK pharmacist must be registered with the General Pharmaceutical Council; membership of the Royal Pharmaceutical Society is no longer sufficient in that regard.

A signatory notification form is available on the PMCPA website (search for 'signatory notification form')

CASE AUTH/2614/7/13

HEALTH PROFESSIONAL v ALLERGAN

Market Research

A health professional and ex Allergan employee complained about market research on injecting botulinum toxins that his wife, a nurse, was asked to participate in.

The complainant noted that the market research asked the recipient to answer questions on all three commercially available botulinum toxins which were referred to by brand name and not their non-proprietary names. The material presented information on a hypothetical, single use, prefilled syringe to be launched shortly and presented calculations on savings to be made through switching to it from a competitor botulinum toxin. Payment for completing the study was a £65 shopping voucher or a cheque.

The complainant assumed that the work had been commissioned by Galderma which marketed Azzalure. The complainant alleged that repeated use of a pharmaceutical company's brand name in material, commissioned by that company, constituted promotion of that product and so the material should carry the prescribing information for that product. The complainant noted that in the market research survey this was not so, in breach of the Code.

The identity of the commissioning pharmaceutical company was not clear from the documentation. The agency confirmed that it was Allergan. Allergan marketed Botox and Vistabel. The complaint was thus taken up with Allergan.

The detailed response from Allergan is given below.

The Panel noted that the complainant had assumed the market research had been commissioned by Galderma, which marketed Azzalure. Whilst the complaint primarily referred to Azzalure it also mentioned other botulinum toxins including Botox and Bocouture [marketed by Merz Pharma]. On being notified of the respondent company, the complainant stated that some of his points should, therefore, be read in context. Allergan was asked to respond to the alleged breaches in relation to its products. The Panel thus considered the complaint on this basis.

The Panel noted Allergan's submission that the purpose of the research was to evaluate the potential opportunity of a ready-to-use neurotoxin (NTX); its value to the facial aesthetic market and to the company. The objectives included exploring reactions etc to new ready-to-use NTXs given potential differences in manufacturing company, available forms, duration of effect and price. To accomplish the stated objectives factors including company/brand were presented to participants systematically to assess market impact. The Panel noted Allergan's late submission that, contrary to its initial statement that Allergan Inc was not researching or developing a R2U toxin, it had entered into a licensing agreement with a Korean company, Medytox to develop and, if approved, commercialize certain NTX products including a potential liquid-injectable product.
The market research asked 120 UK participants about their typical monthly activity regarding cosmetic patients, which brands of NTX they were aware of (Vistabel/Botox, Neuronox, Bocouture, Azzalure, other) and whether if newer, easier to dose/use NTXs became available, they would expand their practice to treat more facial cosmetic patients. The survey continued by asking participants about facial injection locations; choice of brands (Vistabel/Botox, Bocouture, Azzalure) and number of units typically used. Respondents were asked to rate currently available products on a scale of 1 to 6 according to eleven parameters such as 'Does not diffuse outside of targeted tissue', 'Is a brand I can trust' and 'Has excellent overall efficacy'. The market research then presented a series of product profiles sequentially. Each product profile was introduced thus 'Now we would like to show you a potential profile of a new ready-to-use neurotoxin product. Please take a moment to thoroughly read the information. As you read the description please note that this may or may not be the actual profile at launch, but is based on the most recent information on the product available. However, for this research please assume that the information is accurate and that the product will perform as described'. Detailed profiles for Azzalure ready-to-use syringe, Vistabel/Botox ready-to-use vial, Product X (eg Neuronox, Medytox) ready-to-use vial, and Product Z (eg Neuronox, Medytox) a not ready-to-use vial followed. In addition, an alternative profile for Azzalure as a ready-to-use vial was provided and introduced thus: 'Now we would like to get your opinion about an alternative configuration of this new product. The description of this new product that you initially read is only one way this product could be configured in the market and several product attributes could be different'.

Each product profile listed, *inter alia*, the manufacturer, indication, configuration, dosing forms and strengths, duration of effect, dosing and administration, safety/adverse events and the list price. The profiles for products X and Z referred to an established Korean manufacturer and that 'Clinical studies have demonstrated non-inferiority to Vistabel/Botox and no significant difference in the safety profiles'. Participants were then asked about their possible use of the product based on the description. Subsequent questions were based on comparative tables whereby the potential profiles of these 'new product/s' were compared with currently available products. A Vistabel/Botox ready-to-use syringe was mentioned. It was not introduced with a standalone profile although such details appeared

in subsequent comparative tables. The final question asked participants which NTX presentation would be of greatest value to their practice: a ready-to-use vial, current vial requiring reconstitution or a ready-to-use syringe.

The Panel did not accept Allergan's submission that it was made clear that participants were providing feedback on hypothetical scenarios. In its view the phrase 'a potential profile' implied that some features might relate to a prospective product. This was compounded by the provision of a detailed product profile to include the list price and the phrase 'please note that this may or may not be the actual profile at launch'. There was no reference to the wholly hypothetical nature of the profiles in the introduction to the market research. In addition, the Panel noted that the profile of the Azzalure ready-to-use vial was introduced as 'an alternative configuration of this new product' and the product description was not 'the only way this product could be configured in the market and several product attributes could be different'. In the Panel's view this description implied that a product or closely similar product would become available.

The Panel was concerned that when participants were asked to rate products from 'would perform very poorly' to 'would perform very well' in relation to a number of features, the first quantities listed for Vistabel/Botox ready-to-use vial and ready-to-use syringe were 'Would have excellent overall efficacy' and 'Would be able to count on the brand to deliver patient satisfaction'. The corresponding question for Azzalure ready-to-use syringe listed the lower impact statements 'Brand would be profitable to my practice' and 'Would be a brand I trust' as the first and second statements respectively. Excellent overall efficacy and patient satisfaction were lower down the list.

Overall the Panel considered that the market research went beyond its stated objectives and would solicit interest in the botulinum toxins cited including ready-to-use toxins and was promotional in this regard. Participants were asked to assume that the ready-to-use products would become available and state how likely they would be to use them. The Panel considered that insofar as the market research promoted the botulinum toxins cited it also promoted Vistabel/Botox. If this were not so then the effect would be for companies to cite a number of products as a means of avoiding the restrictions in the Code. The Panel considered that as the material promoted Botox and Vistabel relevant prescribing information should have been included; as it was not, a breach of the Code was ruled which was upheld on appeal by Allergan.

The complainant alleged that the material was presented as a 'study' and was clearly market research and not a 'study'. The complainant alleged that repeated use of its prescription only medicine's brand name within this market research by the pharmaceutical company constituted disguised promotion. The complainant further stated that presenting the material as a 'study', paying the participant for completing the market research and presenting arguments aiding a 'switch' from each of the other branded products to Azzalure constituted disguised promotion.

The Panel noted its general comments above and that it considered that as the market research survey promoted Vistabel/Botox, the survey's promotional nature was disguised. A breach of the Code was ruled which was upheld on appeal by Allergan.

The Panel did not, however, consider that the material advocated a switch as alleged and ruled no breach of the Code.

The Panel noted its ruling above and thus considered that the payment of £65 was contrary to requirements of the Code and a breach was ruled which was upheld on appeal by Allergan.

The complainant was concerned that nurses had been targeted to participate in the market research. The indications for all botulinum toxins were the same and Section 4.2 of the Azzalure summary of product characteristics (SPC) read 'Azzalure should only be administered by physicians with appropriate qualifications and expertise in this treatment and having the required equipment'. The complainant submitted that solicited feedback from nurses was therefore solicited feedback from an out of licence group of individuals. The complainant stated that mention of the brand name, Azzalure, comprised 'promotion' and consequently solicited feedback from an out of licence audience on a product referred to by its brand name constituted out of licence promotion.

Lastly, the complainant was concerned that the use of the brand name and a presentation of the product carrying the Azzalure brand name which was not yet available on the market constituted pre-licence promotion.

The Panel noted the complainant's reference to Azzalure in relation to the alleged breach of the Code. The Panel noted, as above, that it was considering this complaint in relation to Vistabel/ Botox. Vistabel/Botox were indicated for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at frown (glabellar lines), in adults <65 years old when the severity of these lines had an important psychological impact for the patient. In addition, Botox had non-cosmetic indications. Each SPC stated that Vistabel/Botox should only be administered by physicians with appropriate qualifications and expertise in the treatment and use of the required equipment. The Panel also noted in a document issued by the MHRA it was noted general cosmetic use was outside the licensed indication of Botox and Vistabel and that for cosmetic use, these medicines could be administered by an appropriate practitioner or anyone acting in accordance with the directions of an appropriate practitioner. An appropriate practitioner was defined as a doctor, a dentist or, subject to certain limitations, *inter alia*, a nurse or pharmacist.

The Panel noted the complainant's concern about the participation of nurses. The Panel was

also particularly concerned that some nurses were selected to participate because they were recommended for participation by nurse colleagues. The Panel noted the market research had been sent *inter alia* to 30 aesthetic nurse injectors. It had also been sent to 30 non injectors all of whom were physicians who would consider a facial aesthetic practice. In addition 40 non-core respondents had received the material including those in ophthalmology and gynaecology and emergency medicine.

The Panel noted that the market research solely covered cosmetic use of the products. Question 1 stated that some questions might refer to uses for all NTXs which were currently not authorized indications. Participants were referred to the prescribing information of each product as to licensed indications. Question 1 referred to the injection of forehead lines, glabellar lines, crows feet, bunny lines, under eyes and lateral eyebrows. The Panel considered that the market research therefore covered the unlicensed use of Vistabel and Botox.

The Panel noted its finding above that the material was promotional and its comments on the products' licensed indications above and the role and participation of aesthetic nurse injectors. The Panel considered that the provision of the material to aesthetic nurse injectors therefore, promoted Botox/ Vistabel for an unlicensed indication as alleged. A breach of the Code was ruled which was upheld on appeal by Allergan.

The Panel noted that the material presented detailed information on and solicited interest in a Botox ready-to-use, single-use vial and syringe. Neither medicine had a licence and thus the Panel considered that they were each promoted contrary to the Code and a breach was ruled which was upheld on appeal by Allergan.

The Panel noted Allergan's late disclosure that it had entered into a licensing agreement with a Korean company, Medytox, to develop and, if approved, commercialize certain NTX products including a potential liquid injectable product. The Panel noted that the products in question were in the mid stages of development. The Panel considered that the survey was, nonetheless, promotional for these unlicensed products referred to in the survey as products X and Z. Comparative claims for both products vs Vistabel/Botox were included. A breach of the Code was ruled which was upheld on appeal by Allergan.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of the Code was ruled which was upheld on appeal by Allergan. Overall, the Panel was very concerned about the market research. The Panel noted its comments about the promotional nature of the material which had been circulated to 120 UK health professionals. The Panel considered that to pay health professionals to participate in a promotional activity brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted its rulings and comments above. The Panel was especially concerned that, in the first instance, it had received incorrect and misleading information. In response to the Panel's question 'Is Allergan Inc researching/developing a ready-to-use neurotoxin?', the company had unambiguously stated that it was not. Allergan subsequently disclosed relevant and contrary information about the activity of Allergan Inc. Allergan had not fully explained why its two submissions were contradictory. In addition the Panel was concerned that the market research was promotional and solicited interest in, *inter alia*, unlicensed medicine/s. Participants had been paid for their time. The Panel noted that the Authority had previously been concerned about the activity of Allergan and market research in Case AUTH/2274/10/09. Taking all the circumstances into account, the Panel reported Allergan to the Code of Practice Appeal Board under Paragraph 8.2 of the Constitution and Procedure for it to consider whether to impose further sanctions.

On appeal by Allergan the Appeal Board noted its submission that when it made its first submission, no-one in the UK knew anything of the Allergan Inc/Medytox deal. As such negotiations were commercially very sensitive, known only to a limited number of very senior employees in the parent organization. As soon as the deal was made public, Allergan had updated the Panel. The Appeal Board noted that market research would often inform commercial decisions but that when conducting such research on the potential of new products, companies had to be extremely careful not to be seen to promote a medicine before the grant of a marketing authorization. In the Appeal Board's view the impact of market research on the participants was important and in that regard it noted that the complainant had considered that the survey at issue was promotional. Nonetheless, the Appeal Board considered that the survey had set out to answer some legitimate business questions and although noting its rulings above, the Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure. No breach of Clause 2 was ruled. The appeal on this point was successful.

In relation to the Panel's report, the Appeal Board noted its rulings above, and in particular the ruling of no breach of Clause 2, and considered that no further action was required.

A health professional and ex Allergan employee complained about market research on injecting botulinum toxins that his wife, a nurse, was asked to participate in.

The complainant noted that the market research asked the recipient to answer questions on all three commercially available botulinum toxins which were referred to by brand name and not their non-proprietary names. The material highlighted the lower price of Azzalure (abobotulinumtoxin A, marketed by Galderma (UK) Ltd) compared with Botox (onabotulinumtoxin A, marketed by Allergan Ltd) and Bocouture (incobotulinumtoxin A, marketed by Merz Pharma UK Ltd). It presented information

on a hypothetical, single use, prefilled syringe to be launched shortly and presented calculations on savings to be made through switching to it from a competitor botulinum toxin. Payment for completing the study was £65 in the form of a shopping voucher for use on the high street or internet, or a cheque.

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The identity of the commissioning pharmaceutical company was not clear from the documentation. The agency confirmed that it was Allergan. Allergan marketed Botox and Vistabel. The complaint was thus taken up with Allergan. When notified of this the complainant was extremely surprised as it did not, in his view, make sense as the positioning of the Galderma product was so positive. The complainant confirmed that he was an ex-employee of Allergan. Given that the responsible company was not Galderma, the complainant stated that some of the points in his complaint might need to be read in context.

When writing to Allergan, the Authority asked it to respond in relation to Clauses 2, 9.1 and 18.1 in addition to 3.1, 3.2, 4.1, and 12.2 cited by the complainant.

* * * * *

1 Prescribing Information

COMPLAINT

The complainant alleged that the material repeatedly used the brand names of three marketed toxins with some pages containing three to four mentions; there appeared to be no attempt to use the non-proprietary name. The complainant stated that a single attempt to identify the product using the brand name was standard in genuine market research. The complainant assumed that the work had been commissioned by Galderma which marketed Azzalure. The complainant alleged that repeated use of a pharmaceutical company's brand name in material, commissioned by that company, constituted promotion of that product and so the material should carry the prescribing information for that product. The complainant noted that in the market research survey this was not so, and he alleged a breach of Clause 4.1.

RESPONSE

Allergan explained that the purpose of the market research was to evaluate the potential opportunity of a ready-to-use (R2U) neurotoxin (NTX). To assess what value a R2U NTX might bring to both the facial aesthetic market and the company it had commissioned market research to better understand the potential size of that opportunity in a number of markets, including the UK. A R2U NTX reduced the need for reconstitution and thus offered ease of administration and increased patient turnaround. These potential new products could be offered by Allergan or a competitor.

Specific research objectives were to:

- Explore physician reactions, perceptions, and receptivity to new R2U products given potential differences in:
  - manufacturing company
  - available forms (vial vs syringe)
  - duration of effect
  - price
- Identify areas of particular strength/shortcoming given currently available options

Understand how a R2U option would impact perceptions of Botox

- Estimate potential demand for a new R2U NTX, including when:
  - it was the only new R2U NTX in the market
  - it was one of two R2U NTXs in the market (assessing order of entry impacts by brand)
  - a low cost NTX was available
- Assess the degree to which an R2U option increased the number of:
  - physicians/injectors interested in/performing facial cosmetic injections
  - units/ml used per patient
  - sites injected per treatment.

To accomplish the central objectives of the research a market evolution discrete choice framework was used. Using this framework the following factors were presented to participants in a systematic fashion to assess market impact:

- manufacturing company/brand
- form
- order of entry
- duration of effect
- price.

Data on current number of patients treated with NTXs in selected areas of the face, including typical mls used in each area, were collected as a baseline reference against which to evaluate changes.

New products were introduced to participants, varying selected characteristics (as outlined in the discrete choice design) and evaluations collected. Participants were then asked to estimate usage across brands (new and current); the allocations were collected at the patient level. Usage, in terms of sites injected and average mls per site, was collected 'outside' of the discrete choice exercise.

A 25-minute online survey was chosen to accomplish the objectives.

The sample comprised of current injectors (physicians and aesthetic nurse injectors) and non-injectors (physicians only) distributed across specialty and representative of the target population. The sample size was chosen as sufficient for the primary purpose of this research (estimation of market potential for new R2U products). The sampling and quantification specific to the UK, along with the screening criteria to qualify to participate in the research was provided.

The physicians were all part of a market research panel who had agreed to be invited to, and participate in, market research.

The majority of nurse injectors were recruited from market research panels. However, as it was difficult to recruit the required number of nurse injectors, those UK nurses who completed the survey were asked to refer other nurses. Eight out of thirty UK nurse respondents were recruited this way and consent to participate in market research was obtained before they were invited to participate in the market research survey. All respondents who came in via the survey link saw the landing page with the terms and conditions that 'opt in' the respondent to participate in market research. The terms and conditions outlined everything that participation in market research entailed and how their responses/data would be used.

ESOMAR (the essential organisation for encouraging, advancing and elevating market research worldwide) and the British Healthcare Business Intelligence Association (BHBIA) recruiting guidelines for market research were followed by all parties involved.

As was standard practice, respondents were offered an appropriate honorarium (£65) to compensate them for their time and feedback.

Allergan enclosed a copy of the contact email invitation and the survey screenshots which included screening questions. The first page of the survey made it clear that participants were participating in a market research survey.

Allergan submitted that the market research was conducted properly and in accordance with the BHBIA Legal and Ethical Guidelines for Healthcare Market Research. The market research material was examined by two final signatories registered with the PMCPA, in line with Section 9.10 of the BHBIA Guidelines and the supplementary information to Clause 14.3. It was considered to be appropriately conducted market research, non-promotional, and therefore did not contravene the Code. As this material was examined, there was no certificate.

Allergan submitted that the following points had been considered and confirmed the appropriate, non-promotional nature of the market research.

There was a clear valid objective to the research which was clear to the potential participants.

Participants comprised of current injectors (physicians and aesthetic nurse injectors) and non-injectors (physicians) distributed across specialty and representative of the target population. The numbers selected from each specialty grouping was small; the largest group size was 40 and covered a very broad range of specialties. Allergan provided details of the 120 respondents.

The sample size was chosen as sufficient for the primary purpose of this research (estimation of market potential for new R2U products).

It was an entirely on-line market research activity. The email and survey screen had been provided and Allergan submitted that these were not promotional in appearance.

Products and brand names were included in this market research. However, given the objective of the research (as described above) it was essential that these were included to achieve the objective of the research. This use of brand names in the research was in line with Section 9.4.1 of the BHBIA Guidelines and did not constitute disguised promotion.

Questions regarding the R2U products were constructed within a market evolution discrete choice framework. The factors to be assessed were presented to participants in a systematic fashion to assess market impacts. When applicable, it was made clear to the participants that they were providing feedback on hypothetical scenarios and potential new products profiles which might (or might not) be the actual profile at launch. At the start of the survey some general questions were asked. It was clearly flagged that some questions might refer to uses for NTXs which were currently not authorized indications. The content of the research was in line with Sections 9.6 and 9.7 of the BHBIA Guidelines and did not constitute disguised promotion.

In response to the specific allegation Allergan acknowledged that products and brand names had been included in the market research but stated that it was essential that these were included to achieve the objective of the research. This use of brand names in the research was in line with Section 9.4.1 of the BHBIA Guidelines and did not constitute disguised promotion. The content did not constitute promotional material or require prescribing information for any of the products mentioned. Allergan denied a breach of Clause 4.1.

In response to a question from the Panel, Allergan submitted that Allergan Inc was not researching/developing a R2U NTX. The purpose of this research was to understand the impact an R2U NTX might have on the market and to help shape future strategy. In relation to the Panel's question about other companies' activities in this regard, Allergan stated that according to www.clinicaltrials.gov there were two studies, one of which was active (but not recruiting) and the other which had completed. Both of these studies were with Dysport R2U (marketed by Ipsen Ltd). The former in cervical dystonia and the latter in glabellar lines.

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Subsequent to the Panel's consideration of this matter, but before it had finalized its rulings, Allergan wrote to the Authority about a recent financial announcement. It stated that Allergan Inc had just announced that it had entered into a licensing agreement with Medytox, a biopharmaceutical company based in Korea. The licensing agreement granted Allergan exclusive rights worldwide, outside of Korea, to develop and, if approved, commercialize certain NTX products, including a potential liquid-injectable product. The close of this transaction was contingent on obtaining certain government approvals. At this time, Allergan anticipated that the transaction would be completed in late 2013 or early 2014. The NTX products included in this

licensing agreement were currently in the mid-stages of development. Allergan stated that it was unaware of this information when it responded previously but considered it should make the Authority aware of this new development.

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PANEL RULING

The Panel noted that the complainant had assumed the market research had been commissioned by Galderma, which marketed Azzalure. Whilst the complaint primarily referred to Azzalure it also mentioned other botulinum toxins including Botox and Bocouture. When notified of the respondent company, the complainant stated that some of his points should, therefore, be read in context. Allergan was asked to respond to the alleged breaches in relation to its products. The Panel thus considered the complaint on this basis.

The Panel noted that the market research had been undertaken in a number of markets including the UK. The Panel noted that the use of the market research in the UK had to comply with the UK Code.

The Panel noted Allergan's submission that the market research was in line with the BHBIA Legal and Ethical Guidelines for Healthcare Market Research. The Panel's role was to consider the complaint in relation to the ABPI Code. It had no role in deciding whether the survey was in line with the BHBIA Guidelines.

Only Clause 12.2 of the Code specifically mentioned market research and it required that market research activities, clinical assessments, post-marketing surveillance and experience programmes, post-authorization studies (including those that were retrospective in nature) and the like must not be disguised promotion. They must be conducted with a primarily scientific or educational purpose. The supplementary information to Clause 12.2 referred to the BHBIA Guidelines. The Panel considered that market research had to be conducted for a bona fide purpose. If market research was ruled to be disguised promotion contrary to Clause 12.2, any payment was likely to be in breach of Clause 18.1. In addition, the company should be mindful of the impression created by the invitation to participate in the survey and by the description of any payment.

The Panel noted Allergan's submission that the purpose of the research was to evaluate the potential opportunity of a R2U NTX; its value to the facial aesthetic market and to the company. The objectives included exploring reactions etc to new R2U NTXs given potential differences in manufacturing company, available forms, duration of effect and price. To accomplish the stated objectives factors including company/brand were presented to participants in a systematic fashion to assess market impact. The Panel noted Allergan's submission that, contrary to its initial statement that Allergan Inc was not researching or developing a R2U toxin, it had entered into a licensing agreement with a Korean company, Medytox to develop and, if approved, commercialize certain NTX products including a potential liquid-injectable product.

The market research questioned the 120 UK participants about their typical monthly activity regarding cosmetic patients, which brands of NTX they were aware of (Vistabel/Botox, Neuronox, Bocouture, Azzalure, other) and whether if newer, easier to dose/use NTXs became available, they would consider expanding their practice to treat more facial cosmetic patients. The survey continued by asking participants about facial injection locations; choice of brands (Vistabel/Botox, Bocouture, Azzalure) and number of units typically used. Questions about variation of dilution levels and use of saline applied to Vistabel and Botox only. Respondents were asked to rate currently available products on a scale of 1 to 6 according to eleven parameters such as 'Does not diffuse outside of targeted tissue', 'Is a brand I can trust' and 'Has excellent overall efficacy'. The market research then presented a series of product profiles sequentially. Each product profile was introduced thus 'Now we would like to show you a potential profile of a new ready-to-use neurotoxin product. Please take a moment to thoroughly read the information. As you read the description please note that this may or may not be the actual profile at launch, but is based on the most recent information on the product available. However, for this research please assume that the information is accurate and that the product will perform as described'. Detailed profiles for Azzalure R2U syringe, Vistabel/Botox R2U vial, Product X (eg Neuronox, Medytox) R2U vial, and Product Z (eg Neuronox, Medytox) a not ready-to-use vial followed. In addition, an alternative profile for Azzalure as a R2U vial was provided and introduced thus: 'Now we would like to get your opinion about an alternative configuration of this new product. The description of this new product that you initially read is only one way this product could be configured in the market and several product attributes could be different'.

Each product profile listed, *inter alia*, the manufacturer, indication, configuration, dosing forms and strengths, duration of effect, dosing and administration, safety/adverse events and the list price. The profiles for products X and Z included statements that the manufacturer was an established Korean manufacturer and that 'Clinical studies have demonstrated non-inferiority to Vistabel/Botox and no significant difference in the safety profiles'. Questions were then asked about the participants' possible use of the product based on the description. Subsequent questions were based on comparative tables whereby the potential profiles of these 'new product/s' were compared with currently available products. A Vistabel/Botox R2U syringe was mentioned. It was not introduced with a standalone profile although such details appeared in subsequent comparative tables. The final question asked participants which NTX presentation would be of greatest value to their practice: a R2U vial, current vial requiring reconstitution or a R2U syringe.

The Panel noted that market research was a legitimate business activity which, to comply with the Code, must not be disguised promotion. The Panel did

not accept Allergan's submission that it was made clear that participants were providing feedback on hypothetical scenarios. In its view the phrase 'a potential profile' did not make it sufficiently clear that the profile was purely hypothetical and implied that at the very least some features might relate to a prospective product. This was compounded by the provision of a detailed product profile to include the list price and the phrase 'please note that this may or may not be the actual profile at launch'. There was no reference to the wholly hypothetical nature of the profiles in the introduction to the market research. In addition, the Panel noted that the profile of the Azzalure R2U vial was introduced as 'an alternative configuration of this new product' and the product description was not 'the only way this product could be configured in the market and several product attributes could be different'. In the Panel's view this description implied that a product or closely similar product would become available.

The Panel was concerned that in relation to a question which required participants to rate a product from 'would perform very poorly' to 'would perform very well' in relation to a number of features, the first quality listed for Vistabel/Botox R2U vial and subsequently Vistabel/Botox R2U syringe was 'Would have excellent overall efficacy', followed by 'Would be able to count on the brand to deliver patient satisfaction'. The corresponding question for Azzalure R2U syringe listed the lower impact statements 'Brand would be profitable to my practice' and 'Would be a brand I trust' as the first and second statements respectively. Excellent overall efficacy and patient satisfaction were the fourth and final statements respectively.

The Panel considered that the cumulative effect of the points mentioned above was that the market research went beyond its stated objectives and would solicit interest in the botulinum toxins cited including R2U toxins and was promotional in this regard. Participants were asked to assume that the R2U products would become available and state how likely they would be to use them. The Panel considered that insofar as the market research promoted the botulinum toxins cited it also promoted Vistabel/ Botox. If this were not so then the effect would be for companies to cite a number of products as a means of avoiding the restrictions in the Code. The Panel considered that as the material promoted Botox and Vistabel relevant prescribing information should have been included; as it was not, a breach of Clause 4.1 was ruled.

APPEAL BY ALLERGAN

Allergan noted the Panel had noted its submission that the market research was in line with the BHBIA Legal and Ethical Guidelines for Healthcare Market Research. The Panel however stated that its role was to consider the complaint in relation to the Code and not to decide whether the survey was in line with the BHBIA Guidelines. Only Clause 12.2 of the Code specifically mentioned market research and it required that market research activities and the like must not be disguised promotion. Market research must be conducted with a primarily scientific or educational purpose. The supplementary information to Clause 12.2 did however refer to the BHBIA Guidelines.

Allergan did not contest that it was the Panel's role to consider the complaint in relation to the Code, more specifically Clause 12.2 in this instance, and that it had no role in deciding whether the survey was in line with the BHBIA Guidelines. Allergan was not asking the Panel to consider whether the survey was in line with the BHBIA Guidelines, but rather whether the survey was in line with Clause 12.2 of the Code.

Allergan noted that Clause 12.2 was the only reference in the Code to 'market research', and in itself it provided no guidance as to what criteria should be applied to ensure that market research complied with Clause 12.2 and was not disguised promotion. Disguised promotion was not defined in the Code. The only clue to this question lay in the supplementary information to Clause 12, which stated 'Attention is drawn to the Legal & Ethical Guidelines for Healthcare Market Research produced by the British Healthcare Business Intelligence Association in consultation with the ABPI'.

Allergan submitted that the Code therefore specifically invited readers to consider the guidelines set out in the BHBIA Code, developed in consultation with the ABPI and so presumably endorsed by it, to help determine whether market research complied with Clause 12.2. It was thus reasonable and proper for Allergan to take these guidelines into account when it designed market research, and it was likewise reasonable and proper for the Panel to consider them when determining whether market research complied with Clause 12.2. To Allergan's knowledge, there were no other available reference guidelines that had been endorsed by the ABPI in the UK, and so this was the only reference on which to rely. Allergan therefore considered the guidelines, as recommended by the supplementary information, when it designed its market research, and now invited the Panel to likewise consider them when it determined whether or not the market research was in line with Clause 12.2.

Allergan submitted that the BHBIA Guidelines aimed to provide clear, comprehensive and explicit best practice guidelines on the execution of primary and secondary healthcare market research within an up-to-date legal and ethical framework. These had been produced by the BHBIA and endorsed by the ABPI (Section 1a) as noted above. The guidelines drew heavily on the Code, the Market Research Society's Code of Conduct and the ICC/ESOMAR International Code of Marketing & Social Research Practice (Section 1c). The Guidelines were designed to:

- set standards for the design, execution and use of market research
- encourage best practice
- provide an industry-sponsored guide for sound and ethical market research
- compliment other relevant professional codes of conduct
- incorporate the impact of relevant legislation and industry guidelines.

Market research attempted to generate understanding and knowledge about a market place and 'consumer or physician' behaviour within it, by gaining information (data) from specific samples of 'consumers or physicians' and extrapolating results to the population as a whole.

Allergan submitted that market research was scientifically-conducted research where the identity of respondents, and all personal data they gave to the researchers, were kept confidential and could not be disclosed or used for any non-research purpose. Market research was not a commercial communication or a selling opportunity.

Allergan submitted that the market research was thus conducted appropriately and in accordance with BHBIA Guidelines to ensure it complied with Clause 12.2 of the Code. The market research material was examined by two signatories registered with the PMCPA, to ensure compliance with Clause 12.2 of the Code. This was also in line with Section 9.10 of the BHBIA Guidelines and the supplementary information to Clause 14.3. It was considered to be conducted for a bona fide reason, was non-promotional and therefore did not contravene the Code.

Allergan submitted that it was evaluating the potential opportunity of a R2U NTX. To assess what need and perceived value an R2U NTX might bring to facial aesthetic health professionals and the company, Allergan commissioned market research to better understand the potential size of that opportunity in a number of markets, including the UK. A R2U NTX reduced the need for reconstitution and thus offered ease of administration and increased patient turnaround. These potential new products could be offered by Allergan or a competitor and, in addition to differences in the market heritage that a manufacturing company could bring to a new R2U product, there were also likely to be differences in the form (vial/syringe), size of the offering (10, 20 and 30 units) due to potential wastage and cost with a single use syringe, duration of effect and price of any product brought to market.

Allergan submitted that Allergan Inc knew that Azzalure/Dysport was being researched/ developed for a R2U formulation; two relevant trials were listed on www.clinicaltrials.gov.

Allergan submitted that the initial market research by Allergan Inc into R2U formulations started in January 2013 with research being fielded in the US and then expanded to other markets. UK field work took place between 13 May and 19 June. Market research and healthcare compliance teams involved in the review, conduct and initial response to the complaint did not know about a Medytox deal until it was publicly announced on 25 September 2013 by Allergan Inc and this information was shared accordingly with the Panel on 1 October. Allergan noted that the material was reviewed and approved for UK use on 26 April 2013.

Allergan submitted that the key objective of the market research at issue was to understand if Allergan Inc should pursue a R2U vial and/or syringe either via internal development or by in-licensing and what impact a competitor R2U vial and/or syringe would have on its current market share. Allergan wanted to:

- Explore physician reactions, perceptions, and receptivity to potential new R2U products given potential differences in manufacturing company, available forms (vial vs syringe), duration of effect and price
- Identify areas of particular strength/shortcoming given currently available options
- Estimate potential demand for a new R2U NTX, including when:
  - Azzalure/Dysport launched first and was the only new R2U NTX in the market
  - Azzalure/Dysport launched first and there were two R2U NTXs in the market — either BOTOX R2U or South Korean R2U (assesses order of entry impacts, given branding)
  - Azzalure/Dysport launched first and there were three R2U NTXs in the market — Botox R2U and South Korean R2U alternating which was the second entrant (assesses order of entry impacts, given branding)
  - A low cost NTX from a South Korean company launched fourth
- Assess the degree to which an R2U option increased the number of:
  - Practitioners interested in performing facial cosmetic injections#
  - Patients being treated

The market research included practitioners who currently practiced in cosmetic medicine.

Allergan submitted that Allergan Inc knew that the Korean manufacturer (Medytox) had a liquid/ R2U formulation in early development but when the market research was conducted, the fact that a potential commercial deal might be possible was not known by any of the corporate head office market research team nor by anyone in the UK office.

Allergan noted that the Panel was concerned that it was not made clear that participants were providing feedback on hypothetical scenarios. In its view the phrase 'a potential profile' did not make it sufficiently clear.

Allergan submitted that the respondents saw the following:

> '*Now we would like* to show you a *potential profile of a new* ***ready-to use*** neurotoxin product. Please take a moment to thoroughly read the information. As you read the description please note that this *may or may not be the actual profile at launch*, but is based on the most recent information on the product available'. (Italics added for emphasis).

Allergan submitted that respondents saw this statement multiple times in the survey and the use of 'potential' and 'at launch' was sufficient to make them aware that these were hypothetical scenarios. At multiple points in the survey, respondents were told that:

> 'Questions refer to uses for all neurotoxins which are currently not authorised indications. Please

always refer to the prescribing information of each product as to licensed indications.'

Allergan noted that the Panel was concerned that in relation to questions which required participants to rate potential product attributes, higher and lower impact statements were ordered preferentially for different products. Allergan submitted that unfortunately this was not apparent in the screen shots of the survey provided to the Panel, but respectively for Q11, Q28b and Q39b these were randomised lists to prevent bias so that every respondent potentially saw a different order of attributes. The original screenshots provided were what one respondent would have seen with the online survey – they would not see the programming flow of the questionnaire such as question skips, randomisation, etc. In reality the responses for these questions were randomised lists to prevent bias so that every respondent potentially saw a different order of attributes. The programmer notes for the questionnaire, clearly stated that these responses should be randomized. This was clear in the final questionnaire document.

Allergan submitted that in line with BHBIA Guidelines, Section 9.4.1, respondents were exposed to a balanced number of brand names so no one brand was seen more than another.

> 'A specific product needs to be referenced e.g. in brand tracking. If possible, include other brand names, as comparators, to blind the subject's identity and so reduce the risk of promotion',

Given the points noted above, Allergan submitted that this was not promotional activity, that required prescribing information and thus it did not breach Clause 4.1.

COMMENTS FROM THE COMPLAINANT

The complainant stated that although he had initially, wrongly thought that Galderma had commissioned the market research, the principles of the complaint still stood against Allergan which had commissioned the market research and was thus responsible for the way in which it was conducted.

APPEAL BOARD RULING

The Appeal Board noted that market research was a legitimate business activity which, to comply with Clause 12.2 of the Code, must not be disguised promotion.

The Appeal Board noted that the market research at issue had originated in the US. Allergan UK was instructed by its parent company in the US, Allergan Inc, to implement the market research in the UK after what Allergan's representatives described as appropriate geographical modifications.

The Appeal Board noted Allergan's submission that the purpose of the research was to evaluate the potential effect of new R2U NTXs given potential differences in manufacturing company, available forms (vial vs syringe), duration of effect and price. The market research questioned the 120 UK participants about their typical monthly activity regarding cosmetic patients, which brands of NTX they were aware of (Vistabel/Botox, Neuronox, Bocouture, Azzalure, other) and whether if newer, easier to dose/use NTXs became available, they would consider expanding their practice to treat more facial cosmetic patients.

The Appeal Board noted one question of the survey which concerned a 'Vistabel/BOTOX Ready-to-use VIAL' stated 'Now we would like to show you a potential profile of a new ready-to-use neurotoxin product. Please take a moment to thoroughly read the information. As you read the description please note that this may or may not be the actual profile at launch, but is based on the most recent information on the product available. However, for this research, please assume that the information is accurate and that the product will perform as described'. This page went on to list product name, manufacturer, product description, indication, product configuration, dosing forms and strengths, duration of effect, dosing and administration, safety/AEs [adverse events] and list price per 50 units. Similar pages were also included for Azzalure New Syringe and Neuronox (product X RTU and Product Z, a not ready-to-use vial). The Appeal Board noted that under 'Dosing Forms and Strengths' it stated 'preservative-free 0.9% Sodium Chloride Injection USP'. The Appeal Board noted that USP was the abbreviation of 'United States Pharmacopoeia', and considered that this should have been modified for the UK audience.

The Appeal Board was concerned about the use of brand names in the market research survey in question. These were used for hypothetical formulations of existing medicines. The Appeal Board queried why these were necessary as they could have been named A,B or C etc. In that regard the Appeal Board noted that Neuronox was denoted as product X or Y depending on its configuration and yet it was still considered necessary to name its manufacturer and include product names. The Appeal Board also questioned whether it was necessary to mock up a hypothetical unlicensed profile of an existing medicine in such detail in the market research in question.

The Appeal Board did not accept Allergan's submission that it was made clear that participants were providing feedback on hypothetical scenarios. In this regard the phrase 'this may or may not be the actual profile at launch' implied that it was not a question of 'if' the product was to be launched but 'when'.

The Appeal Board considered that some of the questions and information were in effect promotional claims for example, stating that the Vistabel/Botox R2U vial 'Allows for flexibility and does not require reconstitution' and the use of coloured text which differentiated new products from existing products.

The Appeal Board considered that the market research would solicit interest in the botulinum toxins cited including R2U toxins and it was promotional in this regard. The Appeal Board considered that as the

material promoted Botox/Vistabel relevant prescribing information should have been included; as it was not, the Appeal Board upheld the Panel's ruling of a breach of Clause 4.1. The appeal on this point was unsuccessful.

2 Disguised promotional activity and payment

COMPLAINT

The complainant alleged that the material was presented as a 'study' and was clearly market research and not a 'study'. The complainant alleged that repeated use of its prescription only medicine's brand name within this market research by the pharmaceutical company constituted disguised promotion. The complainant further stated that presenting the material as a 'study', paying the participant for completing the market research and presenting arguments aiding a 'switch' from each of the other branded products to Azzalure constituted disguised promotion in breach of Clause 12.2.

RESPONSE

Allergan noted its general comments above at point 1. The complainant believed that the market research had been commissioned by another company whose brand was mentioned in the survey, and that the survey promoted this particular product. Whilst Allergan submitted that it could not comment on the alleged promotion of that product, it strongly disagreed that the market research was disguised promotion. The use of the term 'study' in the contact email was appropriate, the term 'study' and 'survey' were used interchangeably in the BHBIA Guidelines. Once participants clicked the link to the 'study', they were taken straight to the introductory screen of the survey which made it clear that it was a marketing research survey.

It was made clear to the participants that they were providing feedback on hypothetical scenarios and potential new products profiles which might (or might not) be the actual profile at launch. At the start of the survey some general questions were asked and it was clearly flagged that some questions might refer to uses for NTXs which were currently not authorized indications. The content of the research was in line with Sections 9.6 and 9.7 of the BHBIA Guidelines and did not constitute disguised promotion. Allergan denied a breach of Clause 12.2.

Noting the additional clauses cited by the Authority, Allergan submitted that the reimbursement offered (£65) was a reasonable compensation for the service provided. It was at a low level, proportionate to the time involved and appropriate to the respondent type and nature of the task. Allergan submitted that this sum would not be an inducement to prescribe, supply, administer, recommend buy or sell any of the products mentioned in the market research. Allergan denied a breach of Clause 18.1.

PANEL RULING

The Panel noted its general comments above at point 1 and that it considered that as the market research survey promoted Vistabel/Botox, the survey's promotional nature was disguised. A breach of Clause 12.2 was ruled.

The Panel did not, however, consider that the material advocated a switch as alleged. The Panel noted its comment above that the material solicited an interest in botulinum toxins including R2U vials and syringes but did not consider that it went beyond such solicitation and positively advocated a switch. In this regard, the complainant had cited Clause 12.2 of the Code and the Panel ruled no breach of that Clause accordingly.

The Panel noted its ruling above of a breach of Clause 12.2. The supplementary information to Clause 18.1, Payment to Individuals, stated that any payment for an activity ruled, *inter alia*, in breach of Clause 12.2 is likely to be viewed as an unacceptable payment. The Panel thus considered that the payment of £65 was contrary to requirements of Clause 18.1 and a breach of that Clause was ruled.

APPEAL BY ALLERGAN

Allergan submitted that the Panel considered that as the market research survey promoted Vistabel/Botox, its promotional nature was disguised. The Panel considered the payment of £65 was contrary to the requirements of the Code as the ruling of a breach of Clause 12.2 would lead to the breach of Clause 18.1.

Allergan submitted that the first screen shot of survey stated:

> 'Thank you for agreeing to participate in this survey. It is a 25 minute *marketing research* survey that we are conducting with a wide range of physician specialties. Your individual answers and identity will be kept confidential. Your opinions will be combined with those provided by others in order to make the best decisions possible. This *survey* is brought to you by [named agency], an independent marketing research firm.' (Italics added for emphasis).

Allergan submitted that it was thus clear from the outset as to the nature of the activity. The use of study in the contact email was also appropriate, as 'study' and 'survey' were used interchangeably in the BHBIA Guidelines. Once the link to the 'study' was clicked it took the participant directly to the introductory screen of the survey which made clear this was a marketing research survey as noted above.

Allergan submitted that the reimbursement of £65 was a reasonable compensation for the service provided. It was at a low level, proportionate to the time involved (25 minutes) and appropriate to the respondent type and nature of the task. This sum would not be an inducement to prescribe one or the other product. The Panel as such did not consider that the material advocated a switch as alleged by the complainant. BHBIA Guidelines, Section 8.24 stated as follows:

> 'Reimbursement (sometimes referred to as an incentive) is any benefit given to a respondent to

encourage their participation in a MR study and should be:
- Kept to a minimum level;
- Proportionate to the amount of their time involved;
- Appropriate to the respondent type and the nature of the task(s).'

Allergan noted that the Panel had noted that the complainant had assumed that the market research was commissioned by Galderma, which marketed Azzalure and that the survey promoted this product. By this, Allergan understood that the Panel had ruled Allergan in breach of Clause 12.2 of the Code for undertaking disguised promotion of a competitor product. Certainly, no complainant had alleged that the market research was disguised promotion of an Allergan product. Allergan queried how it could be found in breach of designing market research that promoted a competitor's product when this would clearly never have been its intention. Allergan had been found in breach of the Code for conducting disguised promotion of a product that competed with its product, subject to a complaint by someone who did not identify Allergan as the promoter, and in circumstances where Allergan clearly would not have had any intention to do so. No complaint had ever been received that Allergan had conducted some form of disguised promotion, and no evidence had been brought to the Panel's attention to suggest that the market research was regarded as disguised promotion, and so Allergan did not understand how the Panel could have reached this conclusion.

Allergan submitted that the complainant alleged and the Panel was concerned about the over use of brand names in the market research survey. Allergan had not used non-proprietary names because there were no differentiating non-proprietary names for the various marketed NTX products in the UK. This could be verified from the respective SPCs of the three products (Vistabel, Bocouture and Azzalure) in the UK. In addition, the various marketed NTX products each had unique characteristics and dosing. To prevent confusion between products it was important to allow respondents to distinguish between brands. The prime objective of the study was to understand the hypothetical use of a R2U vial or syringe for each branded toxin in addition to the current vial.

Furthermore, Allergan submitted that an analysis of the questionnaire provided counts for the number of times each brand appeared associated with a hypothetical or potential new product at each question. The noted questions and counts were:

- Q11. Azzalure was always presented first and was seen by n = 119; no other brands presented at this point.

The Vistabel/Botox brand was presented either second or third, depending on the market scenario selected for the respondent and rotated with the Products X and Z (Medytox / Neuronox branded product):

- Q28b. 60 respondents saw Vistabel before seeing the products X or Z
- Q39b. 59 respondents saw Vistabel after the products X or Z.

Thus, Allergan submitted that looking across both Q28b and Q39b, the Vistabel/Botox brand was presented 119 times, the same number of times as the Azzalure brand and the Korean brand product. Therefore, it was appropriate to use brand names in the survey to allow respondents to correctly respond without confusion. Additionally respondents were exposed to a balanced number of brand names so no one brand was seen more than another. This was further supported by BHBIA Guidelines which stated that brand names could be used when this was essential to the objectives of the research. Section 9.4.1 stated:

'Avoid unnecessary or repeated use of brand names, use 'Product X' unless:
- Reaction to the name or its visual representation is an objective;
- Use of a name is essential to the interpretation of the stimulus, and this is in turn, essential to the study objectives;
- A specific product needs to be referenced e.g. in brand tracking. If possible, include other brand names, as comparators, to blind the subject's identity and so reduce the risk of promotion.'

Allergan submitted that an objective of the survey was to model potential future market scenarios so respondents had to see brand names multiple times. These scenarios that were being determined were:

- Azzalure/Dysport launches first and is the only new R2U NTX in the market
- Azzalure/Dysport launches first and there are two R2U NTX in the market – either Botox R2U or South Korean R2U (assesses order of entry impacts, given branding)
- Dysport launches first and there are three R2U NTX in the market – Botox R2U and South Korean R2U alternating which is the second entrant (assesses order of entry impacts, given branding)
- A low cost NTX from a South Korean company launches fourth.

Allergan submitted that for the research methodology to model all potential scenarios respondents had to see a total of nine product combinations. The methodology used was a discrete choice modeling technique which was typically used to study physician future demand and to predict their responses to a number of hypothetical situations, enabling researchers to forecast the impact of a range of factors such as pricing, product development, and demand etc.

Allergan submitted that this methodology relied on presenting multiple scenarios to respondents to collect sufficient information to build a predictive model. For a discrete choice model, the choice set must meet the following key requirements:

- The set of alternatives must be exhaustive, meaning that the set included all possible alternatives. This requirement implied that the person necessarily chose an alternative from the set.

- The alternatives must be mutually exclusive, meaning that choosing one alternative meant not choosing any other alternatives. This requirement implied that the person chose only one alternative from the set.
- The set must contain a finite number of alternatives.

Allergan submitted the nature of methodology, in the absence of any differentiation with molecule/generic names, required using brand names. Therefore it was appropriate to use brand names in the survey multiple times to allow the survey objectives to be met.

Allergan submitted that the market research questioned 119 UK participants. Sample selection was aimed to represent different specialty groups including dermatologists, plastic/cosmetic surgeons, aesthetic medicine doctors and nurses practising in the cosmetic area. Aesthetic medicine doctors included medical doctors of any primary speciality and dentists practising cosmetic medicine/injecting NTXs. Based on the primary and desk research undertaken by Allergan Inc third party suppliers to determine number of injectors by specialty groups, it showed that this group included a number of different primary specialties including general practitioners.

Allergan submitted that in total, the sample represented 2% of the neurotoxins' cosmetic injector universe, and the sample size only allowed it to analyse results for the total sample (n=119) in a statistically meaningful way, predicting validity of responses with an error margin of up to +/- 9.02% (at 95% confidence interval), but not for different injector groups mentioned above. Considering these factors, a sample of 119 was not unnecessarily large for the objectives of the research. Allergan provided details of the estimated total number of NTX injectors in the UK by speciality group and the percentage of each group included in the survey.

Allergan noted that the BHBIA Guidelines in Section 7b on sample size stated:

- 7.2 The size of the sample must be limited to that necessary to achieve only the objectives of the MR and should be consistent with the nature of the MR undertaken.
- 7.3 There are no fixed guidelines on sample size; this will vary by objective, universe size, analysis requirements, and the level of statistical confidence required. However, if the universe is 800, a sample of 400 could be deemed excessive.
- 7.4 If the sample size is unnecessarily large, the MR may be misconstrued as 'disguised promotion'.

Allergan submitted that as noted above, the survey methodology was discrete choice which required a robust sample to allow study statisticians to build models to simulate the market. Based on the screening methodology all respondents that entered into the survey must be seeing and treating cosmetic patients. Additionally all nurses and physician non-injectors that were not interested in providing aesthetic treatments were screened out. This ensured that all participants were legitimate potential users of NTXs for aesthetic purposes independent of their specialty focus. Therefore it was appropriate to the size of the sample collected across respondent groups to meet the objective of the survey.

Given the points noted above, Allergan did not consider that this was disguised promotion and the payment unacceptable. The company denied breaches of Clauses 12.2 and 18.1.

COMMENTS FROM THE COMPLAINANT

Please see the complainant's comments above (point 1).

APPEAL BOARD RULING

The Appeal Board noted its general comments above at point 1 and that it considered that as the market research survey promoted Vistabel/Botox, the survey's promotional nature was disguised. The Appeal Board upheld the Panel's ruling of a breach of Clause 12.2. The appeal on this point was unsuccessful.

The Appeal Board noted its ruling above of a breach of Clause 12.2. The supplementary information to Clause 18.1, Payment to Individuals, stated that any payment for an activity ruled, *inter alia*, in breach of Clause 12.2 was likely to be viewed as an unacceptable payment. The Appeal Board thus considered that the payment of £65 was contrary to requirements of Clause 18.1 and the Appeal Board upheld the Panel's ruling of a breach of that clause. The appeal on this point was unsuccessful.

3 OUT OF LICENCE PROMOTION

COMPLAINT

The complainant was concerned that nurses had been targeted to participate in the market research. The indications for all botulinum toxins were the same and Section 4.2 of the Azzalure SPC read 'Azzalure should only be administered by physicians with appropriate qualifications and expertise in this treatment and having the required equipment'. The complainant submitted that solicited feedback from nurses was therefore solicited feedback from an out of licence group of individuals. The complainant stated that mention of the brand name, Azzalure, comprised 'promotion' and consequently solicited feedback from an out of licence audience on a product referred to by its brand name constituted out of license promotion in breach of Clause 3.2.

Lastly, the complainant was concerned that the use of the brand name and a presentation of the product carrying the Azzalure brand name which was not yet available on the market constituted pre-licence promotion in breach of Clause 3.1.

RESPONSE

Allergan stated that nurse injectors were selected to participate in the survey so that, together, the respondents reflected the range of specialties of the target population in the UK which might use a R2U NTX.

The legislation surrounding the administration of injectable medicines (such as NTX's) in cosmetic procedures was outlined briefly in a document issued by the MHRA (Frequently asked questions [FAQ]: Supply and administration of Botox, Vistabel, Dysport and other injectable medicines outside their licensed uses such as in cosmetic procedures – November 2012). The MHRA had stated that injectable medication for cosmetic procedures such as NTXs might be: self-administered; administered by an appropriate practitioner (eg doctor, dentist, independent nurse prescriber) or administered by anyone in accordance with the directions of an appropriate practitioner eg a nurse. The prescriber (eg a doctor, dentist or an independent nurse prescriber) had a responsibility to the patient for whom he/she provided a prescription.

Allergan submitted that the selection of nurse injectors to participate in the market research was thus appropriate. More importantly, the market research was not a promotional activity, and therefore did not promote in a manner inconsistent with the SPC and it was not in breach of Clause 3.2.

Allergan submitted that finally, as the market research survey was not promotional it did not agree that it promoted a presentation of a product prior to the grant of its marketing authorisation.

It was made clear to the participants that they were providing feedback on hypothetical scenarios and potential new products profiles which might (or might not) be the actual profile at launch. The content of the research was in line with Sections 9.6 and 9.7 of the BHBIA Guidelines and did not constitute disguised promotion. Therefore, the research was not in breach of Clause 3.2.

In summary, Allergan stated that this market research was conducted properly and in accordance with BHBIA Guidelines. The market research material was examined by two final signatories registered with the PMCPA, in line with Section 9.10 of the BHBIA Guidelines and the supplementary information to Clause 14.3 of the Code. Allergan considered that the survey was appropriately conducted, non-promotional, market research. Allergan denied any breach of the Code including Clauses 9.1 and 2.

PANEL RULING

The Panel noted that the complainant referred to Azzalure in relation to the alleged breach of Clause 3.2. The Panel noted its comment above about the basis upon which it was considering this complaint; namely in relation to Vistabel/Botox. The Panel noted that Section 4.1, Therapeutic Indications, of the Vistabel/Botox SPCs stated that they were indicated for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at frown (glabellar lines), in adults <65 years old when the severity of these lines had an important psychological impact for the patient. In addition, Botox had non-cosmetic indications. Section 4.2 of each SPC required that Vistabel/ Botox should only be administered by physicians with appropriate qualifications and expertise in the treatment and use of the required equipment. The Panel also noted that the MHRA FAQ document cited by Allergan noted general cosmetic use was outside the licensed indication of Botox and Vistabel. Further, the document noted that for cosmetic use, these medicines could be administered by an appropriate practitioner or anyone acting in accordance with the directions of an appropriate practitioner. An appropriate practitioner was defined as a doctor, a dentist or, subject to certain limitations, *inter alia*, a nurse or pharmacist.

The Panel noted the complainant's concern about the participation of nurses. The Panel was also particularly concerned that some nurses were selected to participate because they were recommended for participation by nurse colleagues. The Panel noted the market research had been sent, *inter alia*, to 30 aesthetic nurse injectors. It had also been sent to 30 non injectors all of whom were physicians who would consider a facial aesthetic practice. In addition 40 non-core respondents had received the material including those in ophthalmology and gynaecology and emergency medicine.

The Panel noted that the market research solely covered cosmetic use of the products. Question 1 stated that some questions might refer to uses for all NTXs which were currently not authorized indications. Participants were referred to the prescribing information of each product as to licensed indications. Question 1 referred to the injection of forehead lines, glabellar lines, crows feet, bunny lines, under eyes and lateral eyebrows. The Panel considered that the market research therefore covered the unlicensed use of Vistabel and Botox.

The Panel noted the requirements in the Code for market research as set out above at point 1. Bona fide market research should always be non-promotional. The Panel noted its finding at point 1 that the material was promotional and its comments on the products' licensed indications above and the role and participation of aesthetic nurse injectors. The Panel considered that the provision of the material to aesthetic nurse injectors therefore, promoted Botox/Vistabel for an unlicensed indication as alleged. A breach of Clause 3.2 was ruled.

The Panel noted that it had to consider the allegation about the pre-licence promotion of Azzalure in relation to, *inter alia*, Botox. The Panel noted that the material presented detailed information on and solicited interest in a Botox R2U, single-use vial and syringe. Neither medicine had a licence and thus the Panel considered that they were each promoted contrary to Clause 3.1. A breach of that clause was ruled.

The Panel noted Allergan's disclosure that it had entered into a licensing agreement with a Korean company, Medytox, to develop and, if approved, commercialize certain NTX products including a potential liquid injectable product. The Panel noted that the products in question were in the mid stages of development. The Panel considered that the survey was, nonetheless, promotional for these unlicensed products referred to in the survey

as products X and Z. Comparative claims for both products vs Vistabel/Botox were included. A breach of Clause 3.1 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. Overall, the Panel was very concerned about the market research. The Panel noted its comments about the promotional nature of the material which had been circulated to 120 UK health professionals. The Panel considered that to pay health professionals to participate in a promotional activity brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted its rulings and comments above. The Panel was especially concerned that, in the first instance, it had received incorrect and misleading information. In response to the Panel's question 'Is Allergan Inc researching/developing a ready-to-use neurotoxin?', the company had unambiguously stated that it was not. Allergan subsequently disclosed relevant and contrary information about the activity of Allergan Inc. Allergan had not fully explained why its two submissions were contradictory. In addition the Panel was concerned that the market research was promotional and solicited interest in, *inter alia*, unlicensed medicines. Participants had been paid for their time. The Panel noted that the Authority had previously been concerned about the activity of Allergan and market research in Case AUTH/2274/10/09. Taking all the circumstances into account, the Panel decided to report Allergan to the Code of Practice Appeal Board under Paragraph 8.2 of the Constitution and Procedure for it to decide whether the imposition of further sanctions was appropriate.

APPEAL BY ALLERGAN

Allergan noted the Panel's concern about the participation of nurses and non injectors in the market research activity and that the market research covered the unlicensed use of Botox and Vistabel.

Allergan submitted that nurse injectors were one of the groups selected to ensure distribution of respondents across a range of specialties reflective of the target population in the UK which might use a R2U NTX. This was based on the primary and desk research undertaken by Allergan Inc third party suppliers to determine the number of injectors by specialty groups. It showed that this group included a number of different primary specialties including general practitioners.

Allergan again noted that the legislation surrounding the administration of injectable medicines (such as NTXs) in cosmetic procedures was outlined in the MHRA FAQ document which stated that injectable medicine for cosmetic procedures such as NTXs might be: self-administered; administered by an appropriate practitioner (e.g. doctor, dentist, independent nurse prescriber) or administered by anyone in accordance with the directions of an appropriate practitioner eg a nurse.
Allergan reiterated that the appropriate practitioner (eg a doctor, dentist or an independent nurse prescriber) who prescribed the NTX had a responsibility to the patient for whom he/she had provided a prescription. Therefore, the selection of nurse injectors to participate in the market research was appropriate.

Allergan submitted that the Panel had noted that the MHRA FAQ document stated that the general cosmetic use was outside the licensed indication of Botox and Vistabel. For cosmetic use, these medicines could be administered by an appropriate practitioner or anyone acting in accordance with the directions of an appropriate practitioner. An appropriate practitioner in the MHRA FAQ document was defined as a doctor, dentist or, subject to certain limitations, a nurse or pharmacist.

Allergan submitted that an objective of the survey was to ascertain the likelihood of aesthetic injectors using a R2U NTX (replace usage from the current version that required reconstitution) and to find out if non-neurotoxin aesthetic providers would use NTXs if one that required no reconstitution was available in the future. Allergan submitted that based on the screening methodology all respondents entered into the survey must have seen and treated cosmetic patients. Additionally all nurses and physician non-injectors that were not interested in providing aesthetic treatments were screened out. This ensured that all participants in the survey were legitimate potential users of NTXs for aesthetic purposes independent of their specialty focus.

Allergan submitted that to help find additional aesthetic nurse injectors, identified nurses were asked to refer potential candidates for the research. Only eight nurses out of 29 who participated in the survey were recruited through referral. However all respondents had to go through the screening criteria to enter the survey. Therefore, it was appropriate to use the respondent groups in the survey as they all currently treated aesthetic patients in their practice and could have opted out of the survey.

Allergan submitted that the current injectors of NTXs were screened into the survey if they met the following criteria:

- Must be a physician, nurse practitioner, physician assistant or registered nurse
- More than 75% of clinical practice time spent seeing patients (screener question 6)
- Must typically see at least 10 patients a month for cosmetic consultants and/or treatment
- Must personally inject at least 2 patients per typical month with a NTX for cosmetic consultation and/or treatment
- Must know about Vistabel or Botox
- Nurse injectors who indicated that they were not interested in providing aesthetic treatments in their practice were screened out.

Moreover current non-injectors of NTX were screened into the survey if they met the following criteria:

- Must be a physician – excluded all nurse

practitioners, physician assistants or registered nurses from the non-user sample
- More than 75% of clinical practice time spent seeing patients
- Must typically see at least 10 patients a month for cosmetic consultants and/or treatment – must see at least 10 patients matching this criteria
- Must not currently inject patients with NTX for cosmetic treatment
- Must know about Vistabel or Botox
- Physicians who indicated that they were not interested in providing aesthetic treatments in their practice were screened out.

Allergan submitted that questions which related to current usage were only asked of current injectors and they were warned that:

> 'Some questions may refer to uses for all neurotoxins which are currently not authorised indications. Please always refer to the prescribing information of each product as to licensed indications.'

These questions were only asked to understand if a R2U syringe was made available, what size would be most appropriate for further development as this related to the cost of the product and wastage as a R2U syringe would not be suitable for multiple uses. The intent was never to solicit off-label usage of NTXs for off-label indications. Therefore, it was appropriate to the objective of the survey to collect usage data from current users of NTXs.

Given the points noted above, Allergan did not consider that the market research was out of licence promotion and it denied breaches of Clauses 3.1 and 3.2.

Allergan noted that the Panel was very concerned about the market research and that it had received incorrect and misleading information.

Allergan was extremely disappointed that despite sharing all the information as soon as it was available, the Panel considered that it had received contradictory information. Allergan informed the Panel as soon as an announcement about a possible licensing agreement become public and known to staff in the UK. The reviewers were aware that the research was designed to help the company make strategic business decisions about whether or not to develop an R2U formulation in-house or as it transpired consider entering into such an in-licensing agreement with a third party. However they were not aware of the potential or actual Medytox deal until this was announced on 25 September 2013 with an internal communication to all Allergan employees.

Allergan again noted that it knew that Azzalure/Dysport was being researched/developed for a R2U formulation. According to www.clinicaltrials.gov there were two studies, a Phase III trial in cervical dystonia which was active (but not recruiting) and a completed Phase II trial in glabellar lines. Both of these studies were with Dysport RU. This information was the basis of a potential strategic business decision and in order to help make that informed choice, market research was conducted. The same information was duly shared with the Panel.

As noted above, initial market research into R2U formulations started in January 2013 with research in the US which was expanded to other markets. The material was reviewed and approved for use in UK on 26 April. UK field work took place between 13 May and 19 June. Allergan personnel involved in review, conduct and response to the complaint did not know about the Medytox deal until it was publicly announced on 25 September by Allergan Inc; this information was accordingly shared with the Panel on 1 October.

Allergan submitted that due to the sensitive financial nature of these business in-licensing and/or acquisition deals and their potential impact on the value and stock prices, the information was kept confidential and limited to a core group of Allergan Inc senior executives. Many times the business intelligence and market research teams were asked to provide information and data to support business decision making without knowing the exact nature of any potential business deal. Frequently, as a result of the information gathered, the deals might not be reached. This was a usual business practice and not limited to Allergan or the pharmaceutical industry.

Allergan submitted that at least one of the formulations was not hypothetical as it knew that Dysport/Azzalure was in development and currently in Phase III. It noted however that none of the products were currently available and were not likely to be in the near future. The market research was designed to seek opinions on products that might reasonably be expected to be available in the future. Allergan Inc aimed to assess the potential of a product which still had to enter late phase clinical studies. The intent was to establish the need for strategic future acquisition or partnering or in-house development and required the use of different brand names to effectively assess if the availability of specific brands in a R2U format would differ depending on the specific brand and timing of entry in the market. It was certainly not promotional in intent from Allergan and even the complainant initially considered the survey was commissioned by Galderma for Azzalure.

Allergan submitted that data on the current number of patients treated with NTXs in selected areas of the face, including typical volume used in each area, were collected as a baseline reference against which to evaluate changes.

Allergan outlined the survey design and the composition and size of the sample. Allergan submitted that all the physicians were part of a market research panel of physicians who had agreed to receive solicitations for, and participate in, market research. The numbers selected from each specialty grouping was small; the largest group size was 67 (aesthetic medicine doctors) and covered a

very broad range of specialties based on previous research and available data.

Twenty one of the nurse injectors were recruited from market research panels however, due to the difficulty in recruiting the required number, those UK nurses who completed the survey were asked to refer other nurses. Eight UK nurse respondents were thus recruited through referral and consent to participate in market research was obtained before they were invited to participate. All respondents who came in via the survey link saw the landing page with the terms and conditions that 'opt in' the respondent to participate in market research. The terms and conditions page outlined everything that participation in market research entailed and how their responses/data would be used.

Allergan submitted that, as stated above, it was essential that brand names were included in this market research in order to achieve the specific objective. This use of brand names in the research was in line with Section 9.4.1 of the BHBIA Guidelines and did not constitute disguised promotion as noted below:

9.4.1 **Avoid unnecessary or repeated use of brand names**, use 'Product X' unless:
- Reaction to the name or its visual representation is an objective;
- Use of a name is essential to the interpretation of the stimulus, and this is in turn, essential to the study objectives;
- A specific product needs to be referenced eg in brand tracking. If possible, include other brand names, as comparators, to blind the subject's identity and so reduce the risk of promotion.

Allergan submitted that the questions regarding the R2U products were constructed within a market evolution discrete choice framework. The factors to be assessed were presented to participants in a systematic fashion to assess market impacts. When applicable, it was made clear to the participants that they were providing feedback on hypothetical scenarios and potential new products profiles which might (or might not) be the actual profile at launch. The survey started with some general questions. It was clearly stated that some questions might refer to uses for NTXs which were currently not authorized indications. The content of the research was in line with Sections 9.2 and 9.3 of the BHBIA Guidelines and did not constitute disguised promotion as noted below:

9b Disguised Promotion
Instrument and stimulus design
9.2 **No attempt must be made to influence respondents' opinions or behaviours through the design of the questionnaire, the guide, or the stimulus materials.** This is often referred to as 'disguised promotion', 'selling under the guise of' or 'sugging'. The ABPI Code of Practice 2011 states within Clause 12.2 that: 'MR activities … must not be disguised promotion'.

Impact of the MR
9.3 **Respondents must not be expected, or asked, to make any commitment to change their attitudes or behaviour as a result of the MR**. However, it is reasonable to ask respondents whether a change could hypothetically be possible. This questioning may well be required in new product or sales aid testing e.g. If this product was available and performed as described, would you…..?

Given the points noted above, Allergan did not consider that the rulings of a breach of Clause 2 and 9.1 and the report to the Appeal Board was warranted.

Allergan submitted that since 2009 it had gone beyond the Code requirements to have market research examined including review and approval by two signatories. This check primarily ensured that any proposal was genuine market research, was not promotional and adhered to the relevant Code and industry requirements. Allergan believed this was the case here.

Allergan was very disappointed that its attempt to show complete transparency by providing the Panel with a corporate press release as soon as it became available, had been misinterpreted.

Allergan submitted that this was a piece of genuine market research, it was not promotional and that high standards had been maintained. Allergan denied any breach of the Code.

COMMENTS FROM THE COMPLAINANT

The complainant referred to his comments at point 1 above.

APPEAL BOARD RULING

The Appeal Board noted its finding at point 1 that the material was promotional. The Appeal Board noted that the Allergan representatives could not confirm that the 29 nurses who took the survey were prescribers and suggested that some might administer under the direction of a doctor.

The Appeal Board noted and agreed with the Panel's concerns and comments on the products' licensed indications and the role and participation of aesthetic nurse injectors and decided that the survey promoted Botox/Vistabel for an unlicensed indication as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

The Appeal Board noted that the material presented detailed information on and solicited interest in an Azzalure and Botox R2U, single-use vial and syringe. Neither medicine had a licence and thus the Appeal Board considered that this promoted the Botox R2U, single use vial and syringe contrary to Clause 3.1, and the Appeal Board upheld the Panel's ruling of a breach of that clause. The appeal on this point was unsuccessful.

The Appeal Board noted Allergan's disclosure that it had entered into a licensing agreement with a South Korean company, Medytox, to develop and, if approved, commercialize certain NTX products including a potential liquid injectable product. The survey was promotional for these unlicensed products referred to in the survey as products X and Z. Comparative claims for both products vs Vistabel/ Botox were included. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.1. The appeal on this point was unsuccessful.

The Appeal Board noted that Allergan UK was instructed to undertake the market research by its US parent company. In the Appeal Board's view, when Allergan examined the survey before use it should have changed it to ensure compliance with the Code.

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

The Appeal Board noted Allergan's submission that when it made its first submission, no-one in the UK knew anything of the Allergan Inc/Medytox deal. As such negotiations were commercially very sensitive, they were only known to a limited number of very senior employees in the parent organization. As soon as the deal was made public, Allergan had updated the Panel on the position. The Appeal Board noted that market research would often inform commercial decisions but that when conducting such research on the potential of new products, companies had to be extremely careful not to be seen to promote a medicine before the grant of a marketing authorization. In the Appeal Board's view the impact of market research on the participants was important and in that regard it noted that the complainant had considered that the survey at issue was promotional. Nonetheless, the Appeal Board considered that the survey had set out to answer some legitimate business questions and although noting its rulings above, the Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure. No breach of Clause 2 was ruled. The appeal on this point was successful.

With regard to the Panel's report to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure, the Appeal Board noted its rulings above, and in particular the ruling of no breach of Clause 2, and considered that no further action was required.

Complaint received **4 July 2013**

Case completed **25 January 2014**

ANONYMOUS v NICOVENTURES

Call rates pre-licence

The Medicines and Healthcare Products Regulatory Agency (MHRA) at the request of a complainant referred his/her complaint about call rates for sales teams which was a matter not covered by UK legislation to the PMCPA.

The complainant noted that Nicoventures was currently awaiting a licence for a nicotine replacement therapy (NRT) product and that a reliable source, had informed him/her that the company had set a call rate for health professionals for its sales teams which he/she believed was against the Code in relation to marketing unlicensed products.

The detailed response from Nicoventures is given below.

The Panel noted that Nicoventures was awaiting a marketing authorization for its nicotine-containing product, Voke. The Code allowed those responsible for making policy decisions on budgets to be provided with advance notification of new medicines which would have a significant budgetary impact.

The Panel noted a slide included in a marketing strategy presentation for the healthcare development managers (HDMs) was headed 'Nicoventures Incentive Scheme'. Under a sub-heading of 'Part 1 (GAP analysis): Completion of the following parameters' was listed 'Identification of customers', 'Identification of local guidance documents' and 'Conducting Budget Holder Meetings'. In that regard the Panel noted that a component of the HDMs incentive scheme was linked to conducting meetings. On the left-hand side of the slide, however, it was stated 'No activity measure as a qualifier'. In the Panel's view it was not necessarily unacceptable to include meetings in the HDMs' incentive scheme. The Code recognised that advance notification was appropriate in certain situations; there was no requirement that such information could only be provided reactively.

The Panel considered that as there was no prohibition in the Code with regard to setting call rates for the delivery of advance notification to health professionals, to do so did not, in itself, amount to promotion of a product prior to the grant of a marketing authorization. On the narrow grounds of the complaint, no breach of the Code was ruled. The Panel did not consider that there was any evidence to show that the frequency, time and duration of calls made by the HDMs had caused inconvenience. No breach of the Code was ruled. With regard to call rates the Panel did not consider that the HDMs' briefing material advocated either directly or indirectly any course of action which was likely to lead to a breach of the Code. No breach of the Code was ruled.

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

The Medicines and Healthcare Products Regulatory Agency (MHRA) at the request of a complainant referred his/her complaint to the PMCPA. The MHRA noted that the complaint concerned call rates for sales teams which was a matter not covered by UK legislation. The MHRA also noted that it had recently investigated a complaint that Nicoventures had promoted an unlicensed product to budget holders and it provided a copy of its report on the matter. The complaint to the MHRA was not upheld.

COMPLAINT

The complainant noted that Nicoventures was currently awaiting a licence from the MHRA for a nicotine replacement therapy (NRT) product. It had come to his/her attention, from a reliable source, that Nicoventures had set a call rate for health professionals for its sales teams, in this pre-licence period which he/she believed was against the Code in relation to marketing unlicensed products.

Nicoventures was asked to respond in relation to Clauses 2, 3.1, 9.1, 15.4 and 15.9 of the Code.

RESPONSE

Nicoventures explained that it had performed a thorough investigation and had not issued incentivised activity targets.

Nicoventures explained that it was awaiting a marketing authorization approval from the MHRA for its NRT product, Voke. It was therefore in the pre-licence stage for this product and operated within the guidance of Clause 3.1 of the Code (supplementary information). The only activity which the healthcare development managers (HDMs) were engaged in was that of advance notification of the product to those responsible for making policy decisions on budgets. The HDMs were not telling other health professionals about Voke.

Nicoventures noted that someone had complained to the MHRA earlier in the year and alleged that the company had sought meetings to promote an unlicensed product. Nicoventures provided evidence to the MHRA and the complaint was not upheld.

Nicoventures provided slides which described the HDM incentive scheme; the slides had been approved by the senior management team, certified and presented to the HDM team. The incentive scheme represented a maximum of 10% of their take home pay. The first part of the incentive scheme was based on identifying customers and

local guidance documents, as well as conducting budget holder meetings. The second part was based on a customer completed web-based quality questionnaire. The questions only related to influencing skills, interpersonal and team skills, planning and organisation and business acumen. The activities described in this incentive scheme were the same as the HDMs' objectives in this advance budget notification phase. This was important as the company wanted to stress the types of behaviour that it expected from the team.

The presentation expressly stated that there was no activity measure (call rate or other activity target) as a qualifier for, or as part of, the incentive scheme. Also the activity log for the HDM team showed that the call rate had been low.

At a meeting in July, the sales and marketing team conducted a strategic review of activity and it was clear that the effectiveness of the HDM team was severely hindered by various external parties who encouraged NHS officials to block access to the team. Thus the opportunity for telephone or face-to-face meetings with budget holders was significantly compromised.

As part of this review, the low level of activity within the team was discussed and levels of activity commonly achieved across the industry in the pre-licence and post-licence phase were considered. The regional business directors (RBDs) met with their HDM teams and passed on this information verbally and by email. Unfortunately these communications were not certified and referred to 'contact rates' and 'contact rate targets', despite the fact that it was made clear in the accompanying briefings that these were not incentivised target rates. Neither the objectives nor the incentive scheme were altered.

When the sales team joined in May 2013, Nicoventures expected the product licence to be granted later that year. The company recently learnt that the marketing authorization was unlikely to be granted until 2014.

No summary of product characteristics was available but it would be based on the reference product, the Nicorette inhalator. Nicoventures did not intend to immediately launch the product to prescribers or make it available to the NHS. The product launch would focus initially on consumer sales through pharmacy and retail channels. Consequently, advanced budgetary notification was appropriate for a subsequent NHS launch, and the company expected to focus the activity of its HDMs to pharmacy in the near future. The call rates described in the RBDs' slide deck clearly referred to this. Following receipt of the complaint and the subsequent investigation, an email to clarify the situation regarding objectives and the incentive scheme was sent on 15 October. However, the company had not had feedback from any of its HDMs that they misunderstood that the call rates communicated were formal objectives, incentivised or anything other than an indication of how it hoped activity would pick up in the coming months, given licence approval would make access more straightforward, albeit to a changing customer base. The company had also reminded the RBDs that all material communicating with the HDMs must be approved and certified.

Nicoventures remained vigilant that communication from its management team to the RBDs remained consistent with the Code and it denied breaches of Clauses 2, 9.1, 15.4, and 15.9.

The RBDs and HDMs all had significant experience in the pharmaceutical industry. A condition of joining the company was that they had all passed the ABPI representatives examination and their initial training with Nicoventures included a refresher course on the Code.

In response to a request from the case preparation manager to respond in relation to Clause 3.1 and call rates, Nicoventures reiterated that it did not issue incentivised activity targets for the HDMs. This would not have been appropriate during advance budgetary notification of the product. It was true that it asked the team to arrange advance notification meetings with those responsible for making policy decisions on budgets. At no time were the calls promotional in nature. The company also explained that the HDMs' effectiveness was severely hindered by external parties who encouraged NHS officials to block access to the team, meaning that the opportunity for telephone or face-to-face meetings with budgetary holders was significantly compromised. The HDM team was thus somewhat demoralised and the communications sent to it by the RBDs were intended to motivate and explain what might be possible to achieve once the marketing authorization had been granted and the team could talk to pharmacists. At no time were these illustrations of possible future activity reflected in the HDMs' objectives or their incentive scheme.

Nicoventures believed that the product met the requirements of Clause 3.1. It was a new type of NRT, designed to deliver nicotine in a similar way to a cigarette, and gave smokers the experience they wanted. Other inhaled nicotine products that looked and felt like a cigarette (e-cigarettes), were currently marketed under the General Product Safety Directive. The company anticipated considerable interest in a technology that met the quality, safety and efficacy standards expected of NRT. Nicoventures noted that the product would be the first e-cigarette-like product made in the UK to good manufacturing practice.

Nicoventures anticipated that the product could significantly change costs to the NHS and particularly to local authorities, who since April 2013 had had responsibility for local stop smoking services. It therefore considered that there was a need to provide advance information about the introduction of this new medicine to those responsible for making policy decisions on budgets.

National Institute for Health and Care Excellence (NICE) public health guidance 45, Tobacco: harm-reduction approaches to smoking, issued on 5 June 2013, set out recommendations to reduce the harm from smoking. These recommendations were intended to support and extend the reach of existing stop smoking services. They referred to long-term use

of nicotine-containing products by smokers who might not be able to stop smoking in one step, to those who did not want to give up nicotine or reduce the amount they smoked.

It was accepted that the prevalence of smoking in the UK had not dropped significantly over the last 6 years and that 85% of those who tried to stop smoking had failed to do so at one year. Anything that encouraged smokers to try and to continue to use NRT for as long as they needed it must be seen positively and the company believed that its product would make a significant contribution to this.

In market research conducted last year, in full alignment with the MHRA, its product demonstrated the potential to take market share from tobacco to a greater degree than the Nicorette Inhalator.

In the study, participants were issued a supply of test product (novel device with nicotine dose 0.22mg (low) or 0.45mg (medium)) or Nicorette Inhalator (15mg nicotine). Subjects completed a product market research questionnaire at baseline, and after 3 and 6 days of use (n=574), the data was fed into a market research model enabling modelling of expected market performance of the product and validation against a database of historically tested tobacco products. The study results showed that Voke would have a significant effect on the market and thus gave Nicoventures confidence to make further important manufacturing investment decisions. Nicoventures submitted that the introduction of Voke would increase NHS spending.

Further, the prevalence of smoking in the UK remained stubbornly at about 20% of the adult population. Whilst it was accepted that the best way to reduce the harm of smoking was to stop completely and in one step, for many smokers this could be difficult to achieve, especially for those who were highly dependent on nicotine.

Around two-thirds of smokers stated that they would like to quit or cut down. NICE now recommended that stop smoking advisers and health professionals should advise people to stop smoking in one go, but for those who were not ready or were unable to stop in one step, they should suggest considering a harm-reduction approach. This presented new ways for smokers to change their smoking behaviour, allowing more smokers to be supported by NHS stop smoking services and other healthcare providers in the UK. This would inevitably lead to increased footfall into services and therefore an increased uptake of licensed nicotine-containing products.

Stop smoking services might see the product as a useful addition to the products which could be offered to smokers. Recommendation 6 of the NICE guidance advised those supplying nicotine-containing products to: 'Offer all types of licensed nicotine-containing products to people who smoke, as part of a harm-reduction strategy (either singly or in combination). Take into account their preference and level of dependence'.

A product that smokers wished to use would encourage compliance, helping stop smoking services to meet their targets. Prescription of NRT in line with NICE guidance would help to meet government targets to address health inequality. It was important that budget holders knew about the guidance and the impact a product like Voke could have on their budgets.

To achieve this, Nicoventures had employed a team of HDMs. These individuals were highly experienced, had passed the ABPI examination for representatives and had received refresher training on the importance of complying with Clause 3.1 of the Code, Advance Notification of New Products. They made appointments with local budget holders and policy decision makers, including directors of public health, to discuss the potential impact of tobacco harm reduction and the product on their budgets, using a budgetary implications presentation and a budget impact model (copies were provided). The information contained a brief description of the product in the form of a single slide showing it as a non-branded picture, and further limited factual information about it was only provided on request.

The company stated that it had been fastidious in meeting only budget holders. Its small team of HDMs had provided a suitable background to that field, the NICE guidance and the budgetary impact of introducing the new product.

In response to a request from the Panel for more information, Nicoventures explained that as the complainant referred to a sales team it had used this term in its response. However this team, which had always been referred to internally as a healthcare development team, had always had one objective in the pre-licence phase ie advanced budgetary notification to only those responsible for making NHS strategic and policy decisions on budgets.

The healthcare development team consisted of a number of HDMs managed by 2 RBDs, all of whom were employed by a contract organisation. Nicoventures stated that it used the term 'sales and marketing team' to refer to the team responsible for sales and marketing. Nicoventures provided an organogram to show the relationships between the different personnel.

Nicoventures also provided copies of job descriptions for the HDMs and RBDs and noted that their roles were clearly divided into two phases: 1) pre-licence advanced budgetary notification and 2) post-licence education, product launch and promotion. It had always been intended that the HDMs and RBDs would ultimately become the contract health professional salesforce/business managers, managed by a contract organisation after grant of the product licence. The expectation was for the educational/promotional activity to focus on retail pharmacy after licence grant and then extend to relevant NHS personnel when the product was launched to the NHS.

Nicoventures stated that it had been acutely aware of the scrutiny it would be under given its parent

company, as it sought to build trust in the tobacco harm reduction space. It had therefore been careful to recruit experienced pharmaceutical professionals. The constant message from the top to all employees, especially this important customer-facing contract team, had been that they must operate conservatively and to the highest standards. Nicoventures noted the difficulties they faced in gaining legitimate access to the NHS (following a well-orchestrated external campaign). Despite this, and the natural frustration it caused among such high performing, committed individuals, the company has repeatedly made it clear that its reputation for professionalism came first and that 'call rates' were not something for which they would be incentivised 'pre-licence'.

PANEL RULING

The Panel noted that the complainant had alleged that, by setting call rates for its field force (HDMs) to talk to health professionals about its unlicensed medicine, Nicoventures had breached the Code.

The Panel noted that Nicoventures was awaiting a marketing authorization for its nicotine-containing product, Voke. The supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes stated that NHS organisations needed to be told in advance about medicines which, once marketed, would significantly affect their budgets. The information provided had to be limited to that sufficient to provide a succinct account of the product's properties and directed to those responsible for making policy decisions on budgets rather than those expected to prescribe. Nicoventures had recruited a team of HDMs to provide advance notification of its new product.

The Panel noted a slide included in the marketing strategy presentation for the HDM regional meeting which was headed 'Nicoventures Incentive Scheme'. Under a sub-heading of 'Part 1 (GAP analysis): Completion of the following parameters' was listed 'Identification of customers', 'Identification of local guidance documents' and 'Conducting Budget Holder Meetings'. In that regard the Panel noted that a component of the HDMs incentive scheme was linked to conducting meetings. On the left-hand side of the slide, however, it was stated 'No activity measure as a qualifier' In the Panel's view it was not necessarily unacceptable to include meetings in the HDMs' incentive scheme. The Code recognised that advance notification was appropriate in certain situations; there was no requirement that such information could only be provided reactively.

The Panel considered that as there was no prohibition in the Code with regard to setting call rates for the delivery of advance notification to health professionals, to do so did not, in itself, amount to promotion of a product prior to the grant of a marketing authorization. On the narrow grounds of the complaint, no breach of Clause 3.1 was ruled. The Panel did not consider that there was any evidence to show that the frequency, time and duration of calls made by the HDMs had caused inconvenience. No breach of Clause 15.4 was ruled. With regard to call rates the Panel did not consider that the HDMs' briefing material advocated either directly or indirectly any course of action which was likely to lead to a breach of the Code. No breach of Clause 15.9 was ruled.

The Panel noted its ruling above and did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled. The Panel consequently ruled no breach of Clause 2.

Complaint received **16 September 2013**

Case completed **21 January 2014**

CASE AUTH/2643/10/13

ANONYMOUS CONTACTABLE v PHARMAXIS

Approval of material and provision of training

An anonymous complainant, who described his/her relationship to Pharmaxis as one of contractor to client, referred to a number of matters broadly covering the approval and certification of material and training. The complainant submitted that the company knew about these matters but had failed to act over a period of time.

The detailed response from Pharmaxis is given below.

Pharmaxis marketed two medicines in the UK: Bronchitol (mannitol), indicated as add-on therapy for the treatment of cystic fibrosis (CF) in adults aged 18 years and above (launched 1 June 2012) and Osmohale (mannitol), a diagnostic product indicated for identifying bronchial hyper-responsiveness in subjects with a baseline FEV1 ≥ 70% of predicted (launched December 2007).

The complainant alleged that the company's first standard operating procedure (SOP) or system for approval of non-promotional items was in development in the summer of 2013. Assuming an SOP was now in place, the company had thus operated without a process to approve non-promotional materials for some time during the launch and pre-launch phases of Bronchitol and Osmohale. The complainant alleged that for a number of years non-promotional materials were not subject to any medical check or approval.

The complainant alleged that one of a number of materials which Pharmaxis deemed as non-promotional, and so not subject to medical check, review or sign off, was a journal called Current Medical Literature (CML). CML was an update of the latest information in cystic fibrosis, for which Bronchitol was indicated, and as it was circulated by the representatives it was, contrary to the company's view, promotional. CML included advertisements for Pharmaxis in the pre-launch phase and for Bronchitol after the medicine was licensed. The complainant alleged that CML might have also been promotional in the pre-launch phase given that it was in the cystic fibrosis disease area and included company advertisements.

The complainant stated that the Pharmaxis SOP for the approval of promotional materials included certification of final documents and/or certification of a short print run before the bulk was printed as suggested by the PMCPA. The complainant alleged that if certification was now happening it was a recent change and that it had not happened for some years with regard to Bronchitol or Osmohale. Final versions of materials were not retained until recently (if they were now, which was unclear).

In response to a request for further information, the complainant submitted that he/she did not have copies of the CML journal. The complainant alleged that Pharmaxis representatives had circulated a number of issues over the years. Regardless of whether the latest issue was approved, there would be a number of issues that had not been approved as they did not go through any job bag process. The complainant did not have copies of the promotional SOP which was updated in 2013 and approved by management. The previous version included the certification element which the complainant alleged was never followed. Pharmaxis kept central copies of all SOPs including historical ones. The complainant submitted that he/she did not have a copy of the non-promotional material SOP; his/her complaint was that one did not exist and he/she was not clear if one had been completed and signed off.

The Panel noted that the complainant had firstly made a very general allegation that, contrary to the requirements of the Code, Pharmaxis did not have an SOP or process in place for the approval of non-promotional items for a significant period of time and as such those items were not subject to any medical review or approval. Secondly, the complainant alleged that the CML journals had incorrectly been deemed non-promotional and thus not certified.

The Panel noted that the Code required that certain non-promotional material be certified in a manner similar to that required for promotional items and the supplementary information required that other material issued by companies which related to medicines but which were not intended as promotional material for those medicines *per se*, be examined to ensure that it did not contravene the Code or the relevant statutory requirements.

The Panel noted that the complainant bore the burden of establishing his/her case on the balance of probabilities. The Panel noted Pharmaxis's submission that although it had an SOP, effective from April 2012, which covered the certification of promotional items, both promotional and non-promotional materials were subject to the same rigorous review by two registered final signatories. The Panel further noted Pharmaxis's submission that although at that time there was no certification of non-promotional materials the company did not produce any such materials which required certification. A separate written procedure had been introduced in mid October 2013 to specifically cover proactive approval of non-promotional material. The Panel noted that a judgement had to be made on the available evidence. The Panel did not consider that the complainant had shown, on the balance of probabilities, that in relation to the very general allegation about non-promotional materials, and excluding the CML journal which was dealt with separately below, Pharmaxis had failed to approve

or certify certain non-promotional items and no breach was ruled.

The Panel noted the complainant's second allegation that Pharmaxis had incorrectly characterized, *inter alia*, the CML journal as non-promotional despite it being circulated by representatives and it was thus not subject to medical review or sign off.

The Panel noted Pharmaxis's submission that CML was an educational update prepared and reviewed by an independent editorial board and produced by an independent publisher to provide an abstracting service of major medical journals based around specific therapeutic areas for health professionals. The cystic fibrosis CML was supported by an educational grant from Pharmaxis.

The Panel noted Pharmaxis's submission that it had no input into the editorial content of the journal and was therefore unable to formally approve the content prior to publication. The Panel considered that whilst this might be true for the content of the individual articles, Pharmaxis had placed a single page advertisement in each edition of the journal and had agreed to be the sole sponsor and distributor. The Panel considered that Pharmaxis was inextricably linked to the production of the journal and the company was thus responsible under the Code for the content.

The Panel noted that this matter was further complicated as it appeared that Pharmaxis had not categorized the journal, at the outset, under the Code. Some editions had been certified as promotional whilst others were treated as non-promotional. In the Panel's view it was difficult in such circumstances to maintain compliance. In the absence of any submission on this point the Panel decided on balance that provision of the CML journal should be regarded as a medical and educational good and service (MEGS). The supplementary information to the Code which stated that medical and educational goods must not bear the name of any medicine did not apply to independently produced text books or journals which included, as part of their texts, the names of medicines. MEGS could bear a corporate name.

The Panel examined two volumes of CML; Volume 3, Number 1, with a Bronchitol advertisement after its marketing authorization was granted and before the updated company certification process was implemented, and Volume 3, Number 2, with the same Bronchitol advertisement after the implementation of the updated company certification process. The Panel noted that MEGS were a non-promotional activity. In the Panel's view, the inclusion of the Bronchitol advertisements in CML rendered the journals promotional. They did not satisfy the requirements for MEGS set out in the Code. CML Volume 3, Number 1 had not been certified and thus a breach of the Code was ruled. CML Volume 3, Number 2 had been certified. However, it had not been certified as a non-promotional MEGS and a breach of the Code was thus ruled.

The complainant alleged that CML might be promotional in the pre-launch phase given it was in the disease area and included company advertisements. The Panel examined Volume 1, Number 1, 2011 of CML which was produced before the launch of Bronchitol. It contained an advertisement on the back page that had the company logo at the top with the strapline 'innovation for life' followed by 'Innovation in Respiratory Medicine'. The Panel considered that it was a corporate advertisement and the journal did not directly or indirectly promote Bronchitol before the grant of its marketing authorization as alleged. No breach of the Code was ruled on this narrow point. The Panel noted that whilst MEGS could contain a company name it queried whether they could contain a corporate advertisement which went beyond a mere reference to the company name. The Panel noted that whilst the journal did not promote Bronchitol, it nonetheless required certification as a MEGS. The journal had not been so certified and a breach of the Code was thus ruled.

The Panel noted that representatives had not distributed the journal to health professionals as alleged but had provided them with a card via which a health professional could request a copy of CF CML to be sent directly from head office with a letter giving them the option to unsubscribe from the journal circulation. The Panel noted that the representatives were not provided with any written instructions regarding the circulation of the card. The Panel considered that it would have been helpful if they had been briefed on how the card could be distributed given that they were, in effect, facilitating the distribution of a MEGS. The Panel noted that whilst the complainant had incorrectly referred to distribution of the journals by representatives, he/she had not made any allegations regarding their instruction and in this regard no breach of the Code was ruled.

The Panel noted that the complainant's allegation that certification of final promotional materials had not happened for years and final versions of materials were not retained until recently if they now were which was unclear. The Panel noted that an audit carried out by an external consultant at the request of Pharmaxis revealed that before August 2013 items were not certified in their final form. The Panel ruled a breach of the Code as acknowledged by Pharmaxis.

The Panel noted Pharmaxis's submission that all materials submitted for review were retained and archived for a minimum of 7 years in line with its SOP. The Panel did not consider that the complainant had shown that, on the balance of probabilities, Pharmaxis had failed to preserve all certificates as required and no breach was ruled.

The Panel noted its rulings and considered that high standards had not been maintained. A breach of the Code was ruled. The Panel considered that Pharmaxis's failure to correctly categorize the cystic fibrosis CML as either promotional or non-promotional at the outset, and to thus correctly certify it, displayed a poor understanding of the

Code and that, together with the company's failure to certify the final form of its material, reduced confidence in, and brought discredit upon, the industry. A breach of Clause 2 was ruled.

The complainant further alleged that no Code training was given to staff to keep them up-to-date and many were out of touch. A junior product manager, who was previously a marketing officer, did not have the ABPI examination accreditation despite being in marketing for over two years.

The Panel noted the marketing support officer's role as described in the job description and considered that it failed to satisfy the definition and role of a representative, as defined in the Code, and so the post holder was not required under the Code to take and pass an appropriate ABPI examination. No breach of the Code was ruled which the Appeal Board upheld on the narrow grounds that the complainant had failed to provide any specific evidence to prove his/her complaint.

The Panel noted the complainant's allegation that no Code training was given to keep Pharmaxis staff up-to-date. The Panel noted Pharmaxis's submission that it ensured all staff undertook training on the Code relevant to their particular role via an online learning management system and the UK sales and marketing team members were additionally required to complete Code of Practice courses on an e-learning website. The Panel noted the list of courses completed by Pharmaxis UK sales and marketing team members in the last 18 months which included a course on the scope of the ABPI Code and various SOPs covering aspects of the Code. The Panel further noted Pharmaxis's submission that representatives were provided with current copies of the Code as soon as they became available. The Panel did not consider that Pharmaxis had provided staff with no Code training as alleged and ruled no breach of the Code.

With regard to staff training the Panel noted its rulings above and ruled no breach of the Code including Clause 2.

An anonymous complainant, who described his/her relationship to Pharmaxis as one of contractor to client, complained about a number of matters broadly covering the approval and certification of material and training. The complainant submitted that Pharmaxis was aware of these matters but had failed to act over a period of time.

Pharmaxis marketed Bronchitol (manitol) and Osmohale (manitol). Bronchitol was indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as add-on therapy to best standard of care. Bronchitol was an orphan-designated medicine which was approved through the European centralised procedure on 13 April 2012 and launched in the UK on 1 June 2012. Osmohale was a diagnostic product indicated for identifying bronchial hyper-responsiveness in subjects with a baseline FEV1 ≥ 70% of predicted. It was registered and launched in the UK in December 2007.

1 Approval and certification of material

COMPLAINT

The complainant alleged that contrary to the Code, Pharmaxis did not have a standard operating procedure (SOP) or system for approval of non-promotional items. One was in development in the summer of 2013 and, if it had come into practice, would be signed off by management making the date of its introduction clear. It did not supersede a previous version. The complainant alleged that, assuming an SOP was now in place, the company had operated without one and therefore without a process to approve non-promotional materials for a significant period of time during both the launch and pre-launch phase of Bronchitol. This also applied to Osmohale. The complainant alleged that for a number of years non-promotional materials were not subject to any medical check or approval.

The complainant alleged that Pharmaxis deemed a number of materials as non-promotional and so they were not subject to medical checking or sign off. This included a journal called Current Medical Literature (CML). The complainant explained that CML was an update of the latest information in cystic fibrosis, for which Bronchitol was indicated, and as it was circulated by the representatives it was thus promotional. CML included advertisements for Pharmaxis in the pre-launch phase and Bronchitol advertisements after the medicine had gained a marketing authorization. The complainant alleged that as there was a misunderstanding and no process in place for materials deemed to be non-promotional, CML was exempt from any review. Further, CML was incorrectly assumed to be non-promotional despite being circulated by representatives. The complainant alleged that CML might have also been promotional in the pre-launch phase given that it was in the cystic fibrosis disease area and included company advertisements.

The complainant stated that the Pharmaxis SOP for the approval of promotional materials included certification of final documents and/or certification of a short print run before the bulk was printed as suggested by the PMCPA. The complainant alleged that if certification was now happening it was a recent change and that it had not happened for some years with regard to Bronchitol and Osmohale. Final versions of materials were not retained until recently (if they were now, which was unclear).

In response to a request for further information, the complainant submitted that he/she did not have copies of the CML journal. The complainant alleged that Pharmaxis representatives had circulated a number of issues over the years. Regardless of whether the latest issue was approved, there would be a number of issues that had not been approved as they did not go through a non-promotional or promotional materials job bag, the former of which did not exist at the time. Pharmaxis kept copies of the journal in its literature stores. The complainant did not have copies of the promotional SOP which was updated in 2013 and approved by management. The previous version included the certification element which the

complainant alleged was never followed. Pharmaxis kept central copies of all SOPs including historical ones. The complainant submitted that he/she did not have a copy of the non-promotional material SOP; his/her complaint was that one did not exist. The complainant submitted that one was in development but he/she was not clear if it had been completed and signed off. The complainant submitted that Pharmaxis would be able to provide a copy of this SOP which would detail its inception date and the company could confirm that it was the first SOP for that type of approval.

When writing to Pharmaxis, the Authority asked it to respond in relation to Clauses 3.1, 9.1, 14.1, 14.3, 14.6, 15.9 and 2.

RESPONSE

Pharmaxis was disappointed to receive the complaint. It was committed to complying with both the letter and spirit of the Code and using the Code as a benchmark for its compliance procedures. The company had investigated the aspects of this complaint in detail.

Pharmaxis submitted that it was entirely incorrect to state that there was no medical check of non-promotional items. Before April 2013, when an external consultant was brought in to review all procedures, the approval and certification procedure (SOP/UK/012; effective date 1 April 2012 which replaced SOP/UK/011; effective date 9 November 2007) covered the certification of promotional items only but non-promotional items were subject to the same rigorous review process whilst being created and were reviewed by two final signatories registered with the Medicines and Healthcare Products Regulatory Agency (MHRA) and the PMCPA (one of whom was a medical signatory) before. Pharmaxis submitted that the process was robust and ensured that all materials were thoroughly reviewed in terms of medical accuracy, product licence, form and suitability whether deemed to be promotional or non-promotional. During their review the signatories would determine whether material was promotional or non-promotional and promotional material was certified. Pharmaxis submitted that although at that time there was no certification of non-promotional materials, it did not produce any material listed in Clause 14.3 that required certification. Pharmaxis denied a breach of Clause 14.3.

Pharmaxis embraced the opportunity to continue to improve its processes and in April 2013 an audit of its written procedures relating to all aspects of the Code was undertaken by an external consultant. It was identified that in addition to a written process for the approval of promotional materials (which was in place) a separate written process should be introduced to specifically cover proactive approval of non-promotional material. The new procedure had been approved and was now in place. A copy of the current procedures for the approval of promotional and non-promotional materials was provided.

Pharmaxis submitted that it had an SOP for the approval of promotional materials since the first product was introduced in 2007. Pharmaxis submitted that although a small company, it had developed rapidly since the approval of Bronchitol, its first therapeutic medicine, in 2012. The company realised that it needed external support to ensure that all of its practices complied with the Code and in April 2013 an experienced consultant was employed to review its practices and provide a list of any findings to be addressed by the company. One of the areas identified was certification.

Pharmaxis submitted that it had always had two employees (including a physician) appropriately nominated to the MHRA and PMCPA as 'final' signatories for materials within the job bag process. The audit, however, revealed that certification was taking place at the final artwork stage rather than certification of the final form. Once this omission had been recognised, a revised process was created and the appropriate signatories and support staff trained. Pharmaxis submitted that since August 2013, all materials had followed the revised process through to certification. The certificates and the equivalent job bags would be retained by the company for at least three years after the withdrawal date of the material in compliance with the requirements of Clause 14.6. In addition, a new medical signatory joined the company in July 2013. Pharmaxis submitted that although it now certified the final form of all material, it recognised that pre August 2013 it had not complied with Clause 14.1 and was at that time in breach of that clause.

Pharmaxis submitted that CML was an independent, peer-reviewed, educational publication that had existed for many years. Various editions covered a variety of disease areas and provided an abstracting service of major medical journals based around specific therapeutic areas for health professionals.

The cystic fibrosis CML (CF CML) was prepared and reviewed by an independent editorial board of 8-10 clinical experts from around the world. It was produced by an independent medical education and publishing company. This CML was supported by a grant from Pharmaxis which was the sole sponsor. The publishers approached Pharmaxis with that proposal and a copy of the statement from the publisher confirming that Pharmaxis had no input into the editorial content of CF CML was provided.

Sponsorship opportunities were provided to pharmaceutical companies who could provide the journal to health professionals and place a single page advertisement in each edition. The sponsoring company had no involvement at any stage in the choice of editorial board members, nor did it have any input into the educational content of any volume, including choosing authors of any article within it. In order to maintain the independence of this educational material, no employee of Pharmaxis saw any volume before it was published.

As Pharmaxis had no involvement in developing the content of each CML volume, the company

was unable to formally approve the content prior to publication. The advertisements placed in the journal were all approved via the company approval process and a statement was included in the journal clearly indicating that the company provided financial support. Pharmaxis submitted therefore that the statement from the complainant that 'the material was not subject to any medical checking or sign off' was incorrect.

Pharmaxis submitted that before Bronchitol was launched, it placed a corporate advertisement in CF CML to highlight Pharmaxis' engagement with respiratory medicine. As the corporate advertisement was non-promotional it was not certified, however, it was subject to the medical review process as described above.

During the review process, the medical certifier determined that the initial advertisement proposed for journal inclusion was promotional and therefore inappropriate as it referred to cystic fibrosis. The advertisement was therefore amended during the review process which illustrated that a robust review process was in place as required by the Code. A copy of the rejected advertisement and the comments from the medical certifier were provided.

Pharmaxis considered that it was acceptable to include a corporate advertisement in non-promotional material. There was no mention of Bronchitol, either in the CF CML itself or in the corporate advertisement. Pharmaxis therefore refuted the allegation that the CF CMLs produced pre-launch promoted Bronchitol before the grant of its marketing authorization in breach of Clause 3.1. A copy of the CF CML pre-launch was provided.

Post product launch, CF CML contained a Bronchitol advertisement. Until August 2013, the product advertisement was approved as promotional but as acknowledged above, before August 2013, the company did not complete the final stage of certification of materials as required by the Code. Pharmaxis submitted that the process had since been updated and all materials were now appropriately certified in line with Clause 14.1 including the latest volume of CF CML (Volume 3, Number 2).

Copies of Volume 3, Number 1, with a product advertisement after marketing authorization was granted and before the updated company certification process was implemented, and Volume 3, Number 2, with a product advertisement after marketing authorization was granted and after the updated company certification process was implemented, were provided. For the latter, a copy of the certification document was also enclosed. Pharmaxis volunteered to provide copies of all volumes of the CML if the Authority wanted them.

Pharmaxis submitted that it was the sole distributer of CML. Representatives did not distribute it to health professionals but were provided with a card via which a health professional could request a copy from Pharmaxis head office. The journals were sent directly to the relevant health professional once received by Pharmaxis with a letter giving the health professional an option to unsubscribe from the journal circulation. Pharmaxis submitted that as the request card did not relate to the technical aspects of a medicine which the representatives promoted, no briefing was provided on how the card could be distributed and there was no briefing that advocated, either directly or indirectly, any course of action by a representative which was likely to lead to a breach of the Code. Pharmaxis therefore refuted a breach of Clause 15.9.

Pharmaxis submitted that pre August 2013, although it had thoroughly reviewed and approved promotional material it had not certified the final form and at that time was in breach of Clause 14.1. An internally commissioned review identified this issue and it was addressed as part of a process of continual improvement. Pharmaxis therefore did not consider that it had failed to maintain high standards and was thus not in breach of Clause 9.1. Subsequently Pharmaxis denied that it brought discredit upon, or reduced confidence in the industry and was therefore not in breach of Clause 2.

In response to a request for further information, Pharmaxis submitted that its SOP regarding approval of promotional material created by the European regional office clearly stated that 'The Regional Office will ensure that all materials submitted for review are retained and archived. These should be maintained for a minimum of 7 years'. The term 'materials' related to both the job bag and appropriate accompanying certificates. Pharmaxis submitted that all materials were retained appropriately and denied that any materials had breached Clause 14.6 which required materials and certificates to be preserved for at least three years after use. A copy of the card via which a health professional could request a copy of CF CML was provided.

In response to a request for further information Pharmaxis submitted that when Pharmaxis set up its European operations in the UK, it was decided that it was most appropriate for the company to use the UK Code as its benchmark for compliance. All materials produced by its European office, including those for the UK, were prepared in line with Pharmaxis's understanding of the remit of the Code at that time. This was documented initially in SOP/UK/011 (2007) and then updated in SOP/UK/012 in 2012. However, Pharmaxis launched Bronchitol to its first non-UK European market in 2012 and realised that it needed an additional SOP so that its colleagues in Germany and other countries had guidance on how materials they created or adapted locally would be assessed for compliance and SOP/UK/013, Approval of promotional materials created or adapted by the local companies (Europe), was created. Copies of the SOPs were provided. Pharmaxis apologised for creating confusion with use of its terminology. The SOP for approval of promotional material had always included the need for material to be certified in its final form. The internal audit highlighted the fact that two authorised signatories had been certifying the final artwork rather than the final form. The 'process' was updated in the sense that appropriate staff were retrained on the relevant SOPs and the need for certification of the final form

but no changes to the written process was required as the information was already included in the SOP. Pharmaxis submitted that the need to certify the final form of any piece was also included in the non-promotional material SOP (EU/MED/SOP/MA/0015).

Pharmaxis submitted that as stated in its initial response, although it had always had two personnel (including a physician) appropriately nominated to the MHRA and PMCPA as final signatories, it was aware that before August 2013 certification was taking place at the final artwork stage rather than certification of the final form. In addition Pharmaxis was aware that historically it lacked a separate SOP for non-promotional materials. Both of these issues had been corrected. Pharmaxis submitted that the CF CML Volume 1, Number 1 was reviewed by the medical signatories and deemed to be non-promotional but was not certified. The first volume of CML that was published after August 2013 and thus was fully certified was volume 3, number 2. This volume and the relevant certification materials had been provided with Pharmaxis's initial response. Pharmaxis submitted that the most recent volume (Volume 3, Number 3) had just been received at head office and was currently going through the approval process and would be certified in a similar way to Volume 3, Number 2 before distribution.

Pharmaxis confirmed that CML journals were sent directly from head office to those health professionals who had requested them together with a covering letter, a copy of which was provided. The same letter was sent with each volume of the CML so that health professionals were always made aware that they could unsubscribe from receiving future volumes. Pharmaxis submitted that as the letter was an administrative piece it had not been approved as either promotional or non-promotional.

PANEL RULING

The Panel noted that the complainant had firstly made a very general allegation that contrary to the requirements of the Code Pharmaxis did not have an SOP or process in place for the approval of non-promotional items for a significant period of time and as such those items were not subject to any medical review or approval. Secondly, the complainant alleged that the CML journals had incorrectly been deemed non-promotional and thus not certified.

The Panel noted that Clause 14.3 required that certain non-promotional material be certified in a manner similar to that provided for by Clause 14.1 and the supplementary information required that other material issued by companies which related to medicines but which were not intended as promotional material for those medicines *per se*, be examined to ensure that it did not contravene the Code or the relevant statutory requirements. Non-promotional items requiring certification under Clause 14.3 included educational material for the public or patients, material relating to working with patient organisations, materials prepared in relation to joint working, material relating to patient support programmes and material relating to the provision of medical and educational goods and services (MEGS).

The Panel noted that the complainant bore the burden of establishing his/her case on the balance of probabilities. The Panel noted Pharmaxis's submission that although the SOP, effective from April 2012, only covered the certification of promotional items, both promotional and non-promotional materials were subject to the same rigorous review by two registered final signatories. The Panel further noted Pharmaxis's submission that although at that time there was no certification of non-promotional materials the company did not produce any materials requiring certification as listed in Clause 14.3. A separate written procedure had been introduced in mid October 2013 to specifically cover proactive approval of non-promotional material. The Panel noted that a judgement had to be made on the available evidence. The Panel did not consider that the complainant had shown, on the balance of probabilities, that in relation to the very general allegation about non-promotional materials, and excluding the CML journal which was dealt with separately below, Pharmaxis had failed to approve or certify certain non-promotional material listed in Clause 14.3 as alleged and no breach of Clause 14.3 was ruled.

The Panel noted the complainant's second allegation that Pharmaxis had incorrectly deemed a number of materials including the Current Medical Literature (CML) journal to be non-promotional despite it being circulated by representatives and it was thus not subject to medical review or sign off.

The Panel noted Pharmaxis's submission that CML was an educational update prepared and reviewed by an independent editorial board and produced by an independent publishing company to provide an abstracting service of major medical journals based around specific therapeutic areas for health professionals. The cystic fibrosis CML was supported by an educational grant from Pharmaxis.

The Panel noted that it was possible for a company to sponsor material, produced by a third party, which mentioned its own products, and not be liable under the Code for its content, but only if, *inter alia*, there had been a strictly arm's length arrangement between the parties. In practical terms the arrangements must be such that there could be no possibility that the pharmaceutical company has been able to exert any influence or control over the final content of the material.

The Panel noted Pharmaxis's submission that it had no input into the editorial content of the journal and was therefore unable to formally approve the content prior to publication. The Panel considered that whilst this might be true for the content of the individual articles, Pharmaxis had placed a single page advertisement in each edition of the journal and had agreed to be the sole sponsor and distributor. The Panel considered that Pharmaxis was inextricably linked to the production of the journal and the company was thus responsible under the Code for the content.

The Panel noted that this matter was further complicated as it appeared that Pharmaxis had not categorized the journal, at the outset, under the Code. Some editions had been certified as promotional whilst others were treated as non-promotional. In the Panel's

view it was difficult in such circumstances to maintain compliance. In the absence of any submission on this point the Panel, noting the company's comments about the journal's creation and content, decided on balance that provision of the CML journal should be regarded as a medical and educational good and service (MEGS) as set out in Clause 18.4 of the Code. The supplementary information to that clause stated that the requirement in Clause 18.4 that medical and educational goods must not bear the name of any medicine did not apply where the goods involved consisted of independently produced text books or journals which included, as part of their texts, the names of medicines. MEGS could bear a corporate name. The Panel noted that Pharmaxis had not been asked to respond to Clause 18.4 of the Code. The Panel further noted that Clause 14.1 required MEGS to be certified under Clause 14.3.

The Panel examined two volumes of CML; Volume 3, Number 1, with a Bronchitol advertisement after its marketing authorization was granted and before the updated company certification process was implemented, and Volume 3, Number 2, with the same Bronchitol advertisement after its marketing authorization was granted and after the implementation of the updated company certification process. The Panel noted that MEGS were a non-promotional activity. In the Panel's view, the inclusion of the Bronchitol advertisements in CML rendered the journals promotional. They did not satisfy the requirements for MEGS set out in Clause 18.4 and its supplementary information. CML cystic fibrosis, Volume 3, Number 1 had not been certified and thus a breach of Clause 14.3 was ruled. CML cystic fibrosis Volume 3, Number 2 had been certified. However, it had not been certified as a non-promotional MEGS as required by Clause 14.3. A breach of Clause 14.3 was thus ruled.

The complainant alleged that CML might be promotional in the pre-launch phase given it was in the disease area and included company advertisements. The Panel examined Volume 1, Number 1, 2011 of CML which was produced before the launch of Bronchitol. It contained an advertisement on the back page that had the company logo at the top with the strapline 'innovation for life' followed by 'Innovation in Respiratory Medicine'. The Panel considered that it was a corporate advertisement and the journal did not directly or indirectly promote Bronchitol before the grant of its marketing authorization as alleged. No breach of Clause 3.1 was ruled on this narrow point. The Panel noted that whilst MEGS could contain a company name it queried whether they could contain a corporate advertisement which went beyond a mere reference to the company name. The Panel noted that whilst the journal was not promotional for Bronchitol, it nonetheless required certification as a MEGS. The journal had not been so certified and a breach of Clause 14.3 was thus ruled.

The Panel noted that representatives had not distributed the journal to health professionals as alleged but had provided them with a card via which a health professional could request a copy of CF CML to be sent directly from head office with a letter giving them the option to unsubscribe from the journal circulation. The Panel noted that the representatives were not provided with any written instructions regarding the circulation of the card. The Panel considered that it would have been helpful if the representatives had been briefed on how the card could be distributed given that they were, in effect, facilitating the distribution of a MEGS. The Panel noted the supplementary information to Clause 18.4 explained that material relating to MEGS including, *inter alia*, internal instructions must be certified as required by Clause 14.3. The Panel noted that Pharmaxis had been asked to respond to Clause 15.9 which required that representatives' briefing material on the technical aspects of each medicine promoted was produced and certified. The Panel noted that whilst the complainant had incorrectly referred to distribution of the journals by representatives, he/she had not made any allegations regarding their instruction in this regard. Bearing this in mind and noting its comments above about the relevance of the clause, the Panel ruled no breach of Clause 15.9.

The Panel noted that Clause 14.1 required that promotional material must not be issued unless its final form, to which no subsequent amendments would be made, had been certified by two persons on behalf of the company. The Panel noted that the complainant's allegation that certification of final promotional materials had not happened for years with regard to Bronchitol, Osmohale or Aridol and final versions of materials were not retained until recently if they now were which was unclear. The Panel noted that an audit carried out by an external consultant at the request of Pharmaxis revealed that before August 2013 items were not certified in their final form. The Panel ruled a breach of Clause 14.1 as acknowledged by Pharmaxis.

The Panel noted Pharmaxis's submission that all materials submitted for review were retained and archived for a minimum of 7 years in line with its SOP. The Panel did not consider that the complainant had shown that, on the balance of probabilities, Pharmaxis had failed to preserve all certificates as required by Clause 14.6 and no breach of that clause was ruled.

The Panel noted its rulings and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel considered that Pharmaxis's failure to correctly categorize the cystic fibrosis CML as either promotional or non-promotional at the outset, and to thus correctly certify it, displayed a poor understanding of the Code and that, together with the company's failure to certify the final form of its material, reduced confidence in, and brought discredit upon, the industry. A breach of Clause 2 was ruled.

2 Training

COMPLAINT

The complainant alleged that no Code training was given to staff to keep them up-to-date and many were out of touch. A junior product manager, who was previously a marketing officer, did not have the ABPI examination accreditation despite being in a marketing role for over two years.

When writing to Pharmaxis, the Authority asked it to respond in relation to Clauses 9.1, 16.1, 16.4 and 2 of the Second 2012 Edition of the Code.

RESPONSE

Pharmaxis strongly refuted the complainant's allegation and stated that it had robust systems to ensure all staff were trained on the Code. Pharmaxis had invested significantly to develop an online learning management system (LMS) by which all employees were required to complete training modules relevant to their particular role. The output from the LMS was in the form of a system report which detailed content and date of course completion. A copy of the training record for the employee at issue, a UK marketing support officer, was provided as an example of the training records. Pharmaxis submitted that both field-based and head office staff were set up on the LMS soon after they joined the company.

In addition, all members of the UK sales and marketing team were provided with individual accounts for an e-learning website upon joining Pharmaxis. When new courses on the Code became available, they had to complete them in a timely fashion. Pharmaxis submitted that the e-learning website which it used was well recognised within the pharmaceutical industry as a reputable source of representative training and when a course was completed, the outcome was recorded and a certificate was provided for the individual who had successfully completed the course concerned. Copies of the certificate were added to employees' personal training folders.

A list of courses completed by members of the UK sales and marketing team during the last 18 months was provided. The list had been anonymised to maintain confidentiality but the job role of each individual was marked. In addition, all representatives were provided with hard copies of the Code including updated versions when they became current.

In relation to the representatives' examination, it was a prerequisite that all representatives who joined the company provided documented evidence that they had passed the required ABPI examination; no representative was employed without this qualification. Pharmaxis submitted that whilst it had never been the case, if a representative who had not previously completed the ABPI examination joined the company, it would seek to ensure that they completed it within the timeline specified in Clause 16.4.

Pharmaxis submitted that its four representatives who called on health professionals in relation to the promotion of medicines were experienced and had completed the examination for representatives as outlined in Clause 16.4 before joining the company. Before any job offer was made, candidates had to provide the recruitment agency with documented proof that they had completed the representative's examination.

Pharmaxis submitted that while it was clearly necessary for all representatives to complete the ABPI qualification within the two year time limit, there was no requirement under the Code for employees in a job role outside that of a representative as defined in Clause 1.6 to complete the representatives' examination. It was, however, important that any individual involved in the preparation of marketing materials had some background training on the expectations concerning the Code, even one in a junior role. The individual named by the complainant was not a representative, he/she had completed all the relevant e-learning Code training modules as documented in his/her training record and a copy of his/her job description was provided. The individual also had the most recent Code at his/her workstation for reference.

PANEL RULING

Clause 16.4 of the 2012 Second Edition of the Code stated that the ABPI Medical Representatives Examination must be taken by representatives whose duties comprised or included one or both of calling upon, *inter alia*, doctors and/or other prescribers; and/or the promotion of medicines on the basis of their particular therapeutic properties. The Panel noted that a representative was defined in Clause 1.6 of the Code as someone who called on members of the health professions and administrative staff in relation to the promotion of medicines. In the Panel's view, some employees would not have representative in their job titles but would nonetheless fulfil the role of a representative and would then need to sit and pass an appropriate ABPI examination. The Panel noted the marketing support officer's role as described in the job description and considered that it failed to satisfy the definition and role of a representative, as set out above, and so the post holder was not required under the Code to take and pass an appropriate ABPI examination. No breach of Clause 16.4 was ruled. This ruling was appealed by the complainant.

The Panel noted that Clause 16.1 required all relevant personnel including representatives and members of staff (including persons retained by way of contract with third parties) concerned in any way with the preparation or approval of promotional material, or of information to be provided to members of the UK health professions and to appropriate administrative staff, or of information to be provided to the public and recognised patient organisations to be fully conversant with the requirements of the Code and the relevant laws and regulations. The Panel noted the complainant's allegation that no Code training was given to Pharmaxis staff to keep them up-to-date. The Panel noted Pharmaxis's submission that it ensured all staff undertook training on the Code relevant to their particular role via an online learning management system and the UK sales and marketing team members were additionally required to complete Code of Practice courses on an e-learning website. The Panel noted the list of courses completed by Pharmaxis UK sales and marketing team members in the last 18 months which included a course on the scope of the ABPI Code and various SOPs covering aspects of the Code. The Panel further noted Pharmaxis's submission that representatives were provided with current copies of the Code as soon as they became available. The Panel did not consider that Pharmaxis had provided staff with no Code training as alleged and ruled no breach of Clause 16.1 in that regard.

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

During the consideration of this case, the Panel considered that Pharmaxis should review its procedures to ensure that any information as to changes to the Code etc, including reports of decided cases, were circulated to relevant personnel as detailed in the guidelines on company procedures relating to the Code of Practice.

APPEAL FROM THE COMPLAINANT

The complainant appealed the Panel's ruling of no breach of Clause 16.4 and noted that Pharmaxis had referred to its employee at issue as a UK marketing support officer and provided a job description for that role. The complainant alleged that this was disingenuous and was disappointed that Pharmaxis had not been transparent. The complainant submitted that the Pharmaxis employee was promoted to junior product manager EU and UK some months ago and no job description was created at the time. The Panel stated that the ABPI examination was only relevant to those who performed the duties of a representative. The Pharmaxis employee attended local meetings and other more major events such as meetings of the British Thoracic Society, the European Cystic Fibrosis Society etc where he/she interacted with UK health professionals in a selling role. His/her role was to book and plan the meetings, stands and materials and be present on the stands where he/she interacted with customers in a sales scenario. He/she also booked and attended evening events such as dinners where he/she would interact with customers in a sales situation. Whilst not a representative, he/she performed the same duties as a representative, as expected of any product manager. The complainant appealed the ruling that the Pharmaxis employee did not require the ABPI examination on the basis of his/her role. The complainant urged the Appeal Board to raise the provision of incorrect facts with Pharmaxis.

The complainant alleged that the Pharmaxis employee's objectives for his/her current role, that he/she had been for some months, included a sales focus. This further backed the sales element of his/her role. The objectives were agreed with his/her then manager, who had now left Pharmaxis but the complainant was sure he/she could be contacted if necessary.

The complainant alleged that the Pharmaxis employee performed the duty of a representative not infrequently yet did not have the ABPI examination expected of someone in that position. The complainant alleged that Pharmaxis had incorrectly stated that its employee was a UK marketing support officer; the complainant was disappointed that Pharmaxis had told the Panel incorrect facts. The Pharmaxis employee moved from a UK to a European role and from an administrative officer role to product manager function and with that his/her responsibilities and goals changed to involve direct promotion to customers at exhibitions and congresses where he/she spent significant amounts of time. Regardless of title, the Pharmaxis employee had, and still performed, the duties expected of a representative and given that he/she did not have that background, unlike the majority of junior product managers, then the ABPI examination was a gap that needed to be filled. Pharmaxis had not ensured that this had happened and it had given an incorrect job title to the Panel.

COMMENTS FROM PHARMAXIS

Pharmaxis refuted the allegations that its response had been dishonest.

Pharmaxis submitted that as stated in Clause 1.6, 'The term "representative" means a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines'. As noted by the complainant, its employee attended UK and European congresses, but this was in an organisational capacity, to liaise with stand builders, organise material provision and manage other logistical arrangements. The employee was not responsible for calling on members of the health professions in relation to the promotion of medicines. Pharmaxis acknowledged that its employee would interact with health professionals while on stands at congresses but only for the duration of the congress. However, within his/her current and previous roles its employee had never 'called on' health professionals to promote medicines. As such its employee had been trained on the Code but had not taken the ABPI representatives examination.

Pharmaxis submitted that it had checked previously, and re-checked again recently in light of the complainant's insistence, with two ABPI medical certifiers, both of whom had confirmed that its understanding of the Code in this respect was the same as theirs, and in line with the Panel's ruling of no breach of Clause 16.4.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant noted that Pharmaxis had refuted that it was dishonest. Pharmaxis had not denied, however, that its employee's role changed from an administrative marketing officer to product manager which was the case in point. The complainant submitted that the word dishonest might be incorrect but noted that the point at issue was that Pharmaxis had provided incorrect information to the PMCPA. The role change was relevant to the case and the company's provision of inaccurate information should be kept in mind when any other claims that Pharmaxis had made were assessed.

The complainant noted that Pharmaxis had acknowledged that its employee had interacted with doctors on product promotional exhibition stands. The complainant alleged that product discussions would inevitably take place on the stands by anyone who interacted with those health professionals. Furthermore they also took place at evening events/meals at such congresses and the Pharmaxis employee organised and attended these. The Pharmaxis employee's logistical and organisational function was not in question however the appeal was that he/she interacted with doctors as a representative did whilst at these events. Product discussions would also occur at personal visits to clinicians which were inevitably required in a marketing function.

APPEAL BOARD RULING

The Appeal Board noted that as in all cases, the complainant had the burden of proving his/her complaint on the balance of probabilities. The Appeal

Board considered that the complainant had failed to provide any specific evidence to show that the role of the employee at issue satisfied the definition of a representative given in Clause 1.6 of the Code and that he/she was hence required to take and pass the appropriate ABPI representatives examination. The Appeal Board upheld the Panel's ruling of no breach of Clause 16.4 on this narrow point. The appeal was unsuccessful.

Complaint received **1 October 2013**

Case completed **19 February 2014**

NORGINE v GALEN

Prescribing policy for Laxido Orange

Norgine complained about a prescribing policy document, distributed by Galen, which detailed the process for, and the savings that could be made if patients were switched from Movicol (Norgine's product) to Laxido Orange. Laxido Orange and Movicol had the same qualitative and quantitative active ingredients; both products were used to treat faecal impaction and chronic constipation in adults and children over 12.

Norgine alleged a breach as switch services paid for or facilitated directly or indirectly by a pharmaceutical company were prohibited. It was evident that the document and associated activity related to a switch programme from Movicol to Laxido Orange assisted by third party advisors funded by Galen. Norgine further alleged that high standards had not been maintained.

The detailed response from Galen is given below.

The Panel noted that the prescribing policy document clearly encouraged readers to consider prescribing Laxido Orange where they would otherwise have prescribed Movicol. The document described the qualitative/quantitative composition of the two medicines, briefly reviewed the treatment of constipation and its cost to the NHS and noted that savings could be made by prescribing Laxido Orange instead of Movicol. The document listed a number of ways in which a switch could be implemented and detailed the savings made by such a switch in some primary care organisations (PCOs). It was noted that there were few barriers to change and that these were easily overcome. Readers were invited to contact any one of the five authors, all heads of medicines management or similar, if they had any questions regarding the switch from Movicol to Laxido Orange. The final page of the document featured the Laxido Orange prescribing information.

The Panel noted that although Galen had no editorial input into the document, it had paid the authors and had clearly regarded the material as promotional, it had been certified and included prescribing information. The company had posted the document on its trustsaver website and it had been used in calls with customers.

The Panel noted that the prescribing policy clearly promoted and encouraged readers to switch patients from Movicol to Laxido Orange; this was not unacceptable under the Code. Crucially, Galen did not provide any service to effect or facilitate that switch. Any expense or effort needed to change patients to Laxido Orange had to be borne by the health professional or PCO. The Panel noted Galen's submission that it had not helped to support or assisted any health professional to implement a switch. In that regard the Panel ruled no breach of the Code. The Panel further noted Galen's submission that there was no switch service or programme and in that regard it ruled no breach of the Code. Given these rulings, the Panel did not consider that Galen had failed to maintain high standards and so no breach of the Code was ruled.

Upon appeal by Norgine the Appeal Board noted from Galen that the prescribing policy was suggested by a paid consultant who Galen had employed for other projects. That consultant in turn, and on behalf of Galen, sourced and briefed five NHS pharmacists who were heads of medicines management, or similar, to write the document to illustrate their experience of changing prescribing from Movicol to Laxido Orange. The five pharmacists each received a one-off honorarium from Galen for their input into the document. The Appeal Board noted that Galen had reviewed the document for medical and grammatical accuracy and also to ensure its compliance with the Code.

The Appeal Board noted that the prescribing policy stated that the qualitative and quantitative active ingredients in Movicol and Laxido Orange were the same; Laxido Orange, however, was 20% less expensive than Movicol. The prescribing policy gave clear advice as to how to undertake a switch, described the strategies that the five pharmacists had found successful and the cost savings seen to date. Under a heading 'You can contact us if you have questions', readers were informed that the five pharmacists would be happy to discuss the switch and contact details were provided.

The Appeal Board noted that the supplementary information to the Code stated that switch services paid for or facilitated directly or indirectly by a pharmaceutical company were prohibited. It was further stated that companies could promote a simple switch from one product to another but not to assist a health professional to implement that switch even via a third party.

The Appeal Board queried whether the prescribing policy went beyond simply promoting a switch from Movicol to Laxido Orange. It provided detailed information of strategies to employ, the cost savings that were possible and gave the contact details of five pharmacists who would be willing to discuss the issues involved. In the Appeal Board's view there was a fine line to be drawn between simply promoting a switch and providing so much detailed information in that regard that the information in and of itself facilitated the switch. The Appeal Board recognised that NHS colleagues would talk to each other but was nonetheless concerned that contact details of five pharmacists had been provided. Galen submitted that it had neither requested nor received any feedback from the five pharmacists regarding any communication with their peers. The Appeal Board was concerned that such communication, for

which Galen might be responsible, might facilitate a switch. There was, however, no information before the Appeal Board in this regard. The Appeal Board noted that whilst Galen had provided information as contained in the prescribing policy document, it had not actively assisted any health professional to switch patients from Movicol to Laxido Orange.

The Appeal Board noted its comments above and considered that the prescribing policy was on the limits of acceptability and so, on balance, it upheld the Panel's rulings of no breach of the Code. The appeal was unsuccessful.

Norgine Pharmaceuticals Ltd complained about a document headed 'Prescribing policy: Laxido Orange (macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride) as a relatively straightforward QIPP [quality, innovation, productivity and prevention] saving opportunity – the process and the results' (ref PMR-APR-2013-0093) distributed by Galen Limited. The document detailed the savings that could be made if patients were switched from Movicol (Norgine's product) to Laxido Orange. Laxido Orange and Movicol had the same qualitative and quantitative composition of active ingredients; both products were used to treat faecal impaction and chronic constipation in adults and children over 12.

COMPLAINT

Norgine alleged that the prescribing policy was in breach of Clauses 18.1 and 18.4 which prohibited switch services paid for or facilitated directly or indirectly by a pharmaceutical company. The company further alleged a breach of Clause 9.1 as high standards had not been maintained.

In inter-company correspondence, Norgine noted that on the document at issue, it was stated that the prescribing policy activity had been commissioned and funded by Galen. Norgine considered that it was evident that the document and associated activity related to a switch programme from Movicol to Laxido Orange assisted by third party advisors (eg a head of medicines management, at a local, clinical commissioning group) who had been funded by Galen.

RESPONSE

Galen explained that Laxido Orange contained the same active ingredients as Norgine's product, Movicol and had been approved as a generic medicinal product of Movicol. However, as Laxido Orange was 20% less expensive to buy than Movicol in both 20 and 30 pack sizes, a number of primary care organisations/clinical commissioning groups (PCOs/CCGs) had already changed from prescribing Movicol to prescribing Laxido Orange as it benefitted the NHS in terms of medicine acquisition cost savings and maintained patient care.

Galen submitted that a prescribing policy which shared the experience of changing prescribing from Movicol to Laxido Orange was suggested by a contracted consultant in January 2013. Galen was interested in the suggestion and subsequently agreed the following:

- the consultant would source information from managers who had undertaken such a change in prescribing policy in their region and were willing to share their experience
- Galen would have no editorial input into the content of the document apart from review for medical and grammatical accuracy and to ensure compliance with the Code
- an accurate, honest and balanced document that complied with the Code was to be prepared
- an honorarium (at fair market value) would be paid to the contributing authors by Galen, via the consultant who compiled the document
- engagement of the authors by the consultant/ Galen would not be an inducement to prescribe, supply, administer, recommend, buy or sell any Galen product.

The consultant sourced five independent managers who agreed to share their experience of changing prescribing from Movicol to Laxido Orange due to the cost savings offered to the NHS. Before the medicines managers were approached for their input into the prescribing policy, four trusts had completed a change in prescribing from Movicol to Laxido Orange in their respective regions, while the remaining fifth trust had initiated the process to do so. This was reflected in the following wording which appeared in the prescribing policy:

> 'The undersigned authors have all successfully completed, or are completing, the switch from Movicol to Laxido Orange.'

Agreements, subsequently put in place between Galen and the authors, all stated that Galen's engagement of the authors was not an inducement to prescribe, supply, administer, recommend, buy or sell any Galen product. The authors were paid an honorarium at fair market value for their contribution to the prescribing policy document.

The first draft of the prescribing policy that Galen saw was in early February 2013. However, the contracted consultant and authors did not deem that the document was ready to be entered into the official review process until April. The document then went through a number of draft versions where Galen only reviewed it for medical and grammatical accuracy. Galen had no editorial input into the design and content of the document. This was made clear in the prescribing policy by the statement: 'Galen has had no editorial input apart from review for medical and grammatical accuracy and to ensure compliance with the ABPI Code of Practice'.

The final draft of the document was entered into Galen's approval system on Friday, 10 May, with subsequent certification by two Galen Code signatories on the same day.

The Laxido Orange prescribing policy document was posted as a resource on the Galen trustsaver website (www.trustsaver.co.uk), had been used in calls with customers by Galen health service managers and had been disseminated at company meetings.

Galen noted Norgine's allegation of a breach of Clauses 18.1 and 18.4 and that the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, stated:

> 'Clauses 18.1 and 18.4 prohibit switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine is simply changed to another. For example it would be unacceptable if patients on medicine A were changed to medicine B, without any clinical assessment, at the expense of a pharmaceutical company promoting either or both medicines. It would be acceptable for a company to promote a simple switch from one product to another but not to assist a health professional in implementing that switch even if assistance was by means of a third party such as a sponsored nurse or similar. Such arrangements are seen as companies in effect paying for prescriptions and are unacceptable.'

As noted to Norgine in a letter of 6 August, the prescribing policy document was not part of any switch service/programme. It was simply a retrospective, standalone document through which a number of heads of medicines management shared their best practice experience of changing prescribing of Movicol to Laxido Orange, with their peers. There was no switch service or programme.

Galen stated that it had not at any time helped to support or assisted any health professional to implement a switch. As was permitted under the Code, Galen has used the document to help promote a simple change in prescribing from Movicol to Laxido Orange. The document illustrated that such a change in prescribing was relatively straightforward and could be achieved quickly, that in reality there were no significant barriers to change, and that significant recurring savings could be realised.

In summary, the prescribing policy was a peer-to-peer report which shared best practice on PCOs'/CCGs' experiences in changing prescribing. Galen submitted that it had had no influence over the design and content during drafting and noted that the briefing detailed that the document should be balanced and include negative information if required eg on barriers to change. As stated above, before being contacted by the Galen consultant regarding writing the prescribing policy, four of the five authors had fully completed a change in prescribing from Movicol to Laxido Orange, while the remaining author had initiated the process to do so. Also, a written agreement was in place with the five authors before commencement of the services which clearly stated that their involvement in the prescribing policy was not an inducement to prescribe, supply, administer, recommend, buy or sell any Galen product. Galen had no editorial input into the design and content of the document.

Galen denied a breach of Clauses 18.1 and 18.4. Subsequently, there was also no breach of Clause 9.1. On the contrary, Galen had maintained high standards at all times and its involvement in the production of this document had been carried out in line with the Code and had been made clear and unambiguous. This was illustrated by the clear, prominent declaration statement 'This Prescribing Policy has been commissioned and funded by Galen Limited. Galen has had no editorial input apart from review for medical and grammatical accuracy and to ensure compliance with the ABPI Code of Practice' that appeared on the prescribing policy. This made the extent of Galen's involvement and lack of influence over the material totally clear, in line with Clause 9.10.

Galen considered that the complaint was an attempt by Norgine to discredit an effective and compliant campaign that promoted a medicine which benefitted the NHS in terms of cost savings, and maintained patient care.

PANEL RULING

The Panel noted that the prescribing policy document clearly encouraged readers to consider prescribing Laxido Orange where they would otherwise have prescribed Movicol. The document described the qualitative/quantitative composition of the two medicines, briefly reviewed the treatment of constipation and its cost to the NHS and noted that savings could be made by prescribing Laxido Orange instead of Movicol which would facilitate the QIPP agenda of the NHS. The document listed a number of ways in which a switch could be implemented and detailed the savings made by such a switch in some PCOs. It was noted that there were few barriers to change and that these were easily overcome. Readers were invited to contact any one of the five authors, all heads of medicines management or similar, if they had any questions regarding the switch from Movicol to Laxido Orange. The final page of the document featured the Laxido Orange prescribing information.

The Panel noted that although Galen had no editorial input into the document, it had paid the authors and had clearly regarded the material as promotional, it had been certified in accordance with the Code and it included prescribing information for Laxido Orange. The company had posted the document on its trustsaver website and it had been used in calls with customers.

The Panel noted that the prescribing policy clearly promoted and encouraged readers to switch patients from Movicol to Laxido Orange. As noted in the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, this was not unacceptable under the Code. Crucially, Galen did not provide any service to effect or facilitate that switch. Any expense or effort needed to change patients to Laxido Orange had to be borne by the health professional or PCO. The Panel noted Galen's submission that it had not helped to support or assisted any health professional in implementing a switch. In that regard the Panel ruled no breach of Clause 18.1. The Panel further noted Galen's submission that there was no switch service or programme and in that regard it ruled no breach of Clause 18.4. These rulings were appealed by Norgine.

Given its rulings above, the Panel consequently ruled no breach of Clause 9.1. This ruling was appealed by Norgine.

APPEAL FROM NORGINE

Norgine was extremely disappointed with the Panel ruling and questioned the rationale behind the decision. Norgine challenged the Panel's statement that '… Galen did not provide any service to effect or facilitate that switch' particularly with reference to the Code's clarity on the prohibition of switch programmes; the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, stated 'Clauses 18.1 and 18.4 prohibit switch services paid for or **facilitated directly or indirectly** by a pharmaceutical company whereby a patient's medicine is simply changed to another.' (emphasis added by Norgine).

Norgine alleged that, at the very least, the prescribing policy clearly indirectly facilitated a switch where patients were simply switched from Movicol to Laxido Orange in breach of Clauses 18.1 and 18.4. Galen had indeed indirectly facilitated the switch for clinicians.

Norgine noted that the supplementary information cited above further stated that 'It would be acceptable for a company to promote a simple switch from one product to another **but not to assist a health professional in implementing that switch even if assistance was by means of a third party …'** (emphasis added by Norgine).

Norgine alleged that Galen had assisted prescribers to implement that change as by its admission the prescribing policy facilitated communication between prescribers who had switched and those who had not and provided information and guidance that they would have otherwise had to seek independently to begin to affect that change. Specifically, information on who had experience of such switches and where and how to contact them, and crucially, practical help with planning a switch programme and help with addressing practical issues. The policy detailed the potential methods for effecting the switch and provided specific detailed information on which tools to use to effect the switch in specific regions of the country, it gave detailed advice on overcoming barriers to a switch and provided contact details of named pharmacists who effectively acted as 'facilitators' and who were engaged specifically to provide this information to potential prescribers – if this was not facilitation (at least indirectly) what was?

Norgine noted that Galen had initiated this item, paid for its creation and paid the pharmacists that contributed to it. As such, Norgine alleged these pharmacists were effectively working on behalf of Galen and speaking with its voice, given that they had endorsed the prescribing policy which was clearly promotional and included prescribing information. Norgine found Galen's contention that it had no input into the content of the item difficult to believe given the timescales involved and how the item was finally approved for use.

Norgine noted the time frame for the development of the prescribing policy as provided by Galen:

- The prescribing policy was first 'proposed' in January 2013
- First draft reviewed by Galen on 7 February
- Official review on 10 April
- A number of draft versions where Galen 'only reviewed for medical and grammatical accuracy'
- Final draft reviewed and approved by two Galen signatories on the same day of the review on 10 May.

Norgine alleged that as the review process was effectively almost completely done 'off-line', and that only the final version was uploaded to Galen's copy approval system on the day of certification, it strained credibility to suggest that Galen had no editorial input into the design or content of the document (including addition of prescribing information) from first draft on 7 February to the final version on 10 May (nearly 4 months), where several versions were reviewed (with no evidence provided by Galen of these versions and who provided input into these reviews).

Norgine alleged that Galen's contention that it was approached by a contracted consultant in January 2013 to initiate the prescribing policy was irrelevant. A contracted consultant was a Galen representative for the duration of the contract and the decision to go ahead with the item remained Galen's alone.

Norgine alleged that the prescribing policy was clearly in breach of Clauses 9.1, 18.1 and 18.4 of the Code.

COMMENTS FROM GALEN

Galen noted that Norgine disagreed with the Panel's statement that 'Crucially, Galen did not provide any service to effect or facilitate that switch' and again noted that Clauses 18.1 and 18.4 of the Code prohibited switch services paid for or facilitated directly or indirectly by a pharmaceutical company.

Galen agreed that the Code clearly prohibited switch programmes. However, Galen reiterated that the prescribing policy was not part of any switch service/ programme; it was a retrospective, standalone document through which, a number of heads of medicines management shared, with their peers, their experience of changing the prescribing of Movicol to Laxido Orange. There was no switch service or programme.

Galen noted that Norgine had also quoted the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, which stated 'It would be acceptable for a company to promote a simple switch from one product to another but not to assist a health professional in implementing that switch even if assistance was by means of a third party such as a sponsored nurse or similar.' Galen submitted that in compliance with this, it had used the prescribing policy to help promote a simple change in prescribing from Movicol to Laxido Orange. The document illustrated that such a change in prescribing was relatively straightforward

and could be achieved quickly, that in reality there were no significant barriers to change and that significant recurring savings could be realised.

Norgine had alleged that Galen had assisted prescribers to implement a change in prescribing as the prescribing policy facilitated communication between prescribers who had switched and those who had not and further provided information and guidance that they would have otherwise had to seek independently to begin to affect that change. Specifically, information on who had experience of such switches and where and how to contact them, and crucially, practical help with planning a switch programme and help with addressing practical issues.

Galen submitted that furthermore Norgine had also claimed that the prescribing policy had provided contact details of named pharmacists who effectively acted as 'facilitators' and who had been engaged specifically to provide this information to potential prescribers. Galen submitted that it had never helped to support or assisted any health professional to implement a 'switch'. This included the provision of any financial support or practical assistance. As acknowledged by the Panel, 'Any expense or effort needed to change patients to Laxido Orange had to be borne by the health professional or PCO'.

Galen submitted that the prescribing policy was written by five independent managers who agreed to share their experience of changing from Movicol to Laxido Orange due to the cost savings offered to the NHS. The managers were only engaged by Galen to write the prescribing policy. The inclusion of their names and contact details so that they could address any questions from their peers in relation to their best practice experience of changing prescribing of Movicol to Laxido Orange, was their own decision and entirely reasonable.

Galen submitted that it had never requested or received any reports or feedback from the authors regarding any communication with their peers. It was untrue to claim that these managers acted as 'facilitators' of a switch service or programme that would be prohibited under the Code and wrongly questioned the credibility of these key, experienced NHS pharmacists.

Galen noted that Norgine queried the independence of the document and cited the timelines provided by Galen with regard to the review and approval process. Galen submitted that this was a new issue which Norgine had never questioned previously and that the time over which the document was drafted was irrelevant.

Galen submitted that the prominent and accurate declaration wording contained in the prescribing policy made the extent of its involvement and lack of influence over the material totally clear, in line with Clause 9.10. Galen had been transparent in this regard and firmly disputed the claim that its involvement was any more than declared; had that been the case, the authors would not have allowed their names to be associated with the document. Laxido Orange was a key and successful product for Galen in the UK; the company's continued good relationship with customers and all matters of Code compliance were of utmost importance to it.

Galen submitted that with regard to Norgine's final point, the reference to the contracted consultant in Galen's response above was completely relevant as the PMCPA had requested full details of Galen's involvement in producing and distributing the prescribing policy and Galen had thus answered the PMCPA's question as to who initiated the material.

In summary, Galen submitted that the Panel's rulings in this case were completely unequivocal and Norgine had not provided any new and relevant information in relation to its complaint. The fact remained that the prescribing policy was not part of a switch service or programme. As acknowledged by the Panel, any expense or action required to achieve this lay with the individual health professionals or PCOs and the Laxido Orange prescribing policy was not in breach of Clauses 18.1 and 18.4 of the Code and consequently not in breach of Clause 9.1.

FINAL COMMENTS FROM NORGINE

Norgine did not consider that Galen's comments above added anything new to the discussion in this case.

APPEAL BOARD RULING

The Appeal Board noted from the representatives of Galen that the prescribing policy at issue was suggested to Galen by a paid consultant who it had employed for other projects. That consultant in turn, and on behalf of Galen, sourced and briefed five NHS pharmacists who were heads of medicines management, or similar, to write the document to illustrate their experience of changing prescribing from Movicol to Laxido Orange. Four of the pharmacists had already completed the switch process; the other had yet to do so. The five pharmacists each received a one-off honorarium from Galen for their input into the prescribing policy document. In the Appeal Board's view, although the concept, content and design of the prescribing policy had come from consultants working on behalf of the company, Galen was wholly responsible for the document, in the same way as it would be responsible for any other piece of promotional material. The Appeal Board noted that Galen had reviewed the document for medical and grammatical accuracy and also to ensure its compliance with the Code.

The Appeal Board noted that the prescribing policy stated that the qualitative and quantitative active ingredients in Movicol and Laxido Orange were the same; Laxido Orange, however, was 20% less expensive than Movicol. The prescribing policy gave clear advice as to how to undertake a switch and included a list of bullet points which described the strategies that the five pharmacists had found successful; a table showed the mix of strategies employed by each of the pharmacists in their respective PCOs. A second table detailed the cost savings seen to date in each PCO and there was a

short discussion on barriers to change. Under a heading 'You can contact us if you have questions', readers were informed that the five pharmacists would be happy to discuss the switch from Movicol to Laxido Orange and their contact details (email and telephone) were stated.

The Appeal Board noted that the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, stated that:

> 'Clauses 18.1 and 18.4 prohibit switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine is simply changed to another. For example it would be unacceptable if patients on medicine A were changed to medicine B, without any clinical assessment, at the expense of a pharmaceutical company promoting either or both medicines. It would be acceptable for a company to promote a simple switch from one product to another but not to assist a health professional in implementing that switch even if assistance was by means of a third party such as a sponsored nurse or similar. Such arrangements are seen as companies in effect paying for prescriptions and are unacceptable.'

The Appeal Board noted the content of the prescribing policy and queried whether it went beyond simply promoting a switch from Movicol to Laxido Orange. It provided the reader with detailed information of strategies to employ, the cost savings that were possible and gave the contact details of five pharmacists who would be willing to discuss the issues involved. In the Appeal Board's view there was a fine line to be drawn between simply promoting a switch and providing so much detailed information in that regard that the information in and of itself facilitated the switch. The Appeal Board recognised that NHS colleagues would talk to each other but was nonetheless concerned that contact details of five pharmacists had been provided. Galen submitted that it had neither requested nor received any feedback from the five pharmacists regarding any communication with their peers. The Appeal Board was concerned that such communication, for which Galen might be responsible, might facilitate a switch. There was, however, no information before the Appeal Board in this regard. The Appeal Board noted that whilst Galen has provided information as contained in the prescribing policy document, it had not actively assisted any health professional in implementing a switch for patients on Movicol to Laxido Orange.

The Appeal Board noted its comments above and considered that the prescribing policy was on the limits of acceptability and so, on balance, it upheld the Panel's rulings of no breach of Clauses 18.1 and 18.4 and consequently upheld the ruling of no breach of Clause 9.1. The appeal was unsuccessful.

Complaint received **21 October 2013**

Case completed **15 January 2014**

PATIENT v AMGEN and GLAXOSMITHKLINE

Patient information on Prolia

A patient who had been prescribed Prolia (denusumab) complained about the information which Amgen UK had supplied about the medicine. Prolia was indicated, *inter alia*, for the treatment of osteoporosis in postmenopausal women at increased risk of fractures. The matter was subsequently taken up with GlaxoSmithKline UK which co-promoted Prolia.

The complainant explained that in August 2012, she received an injection of Prolia at a local hospital. Before agreeing to treatment she had been told that the only side effects were those listed in the leaflet issued by a national patient support group. The complainant submitted that this leaflet was inaccurate.

Upon receiving treatment the complainant was given a German package leaflet and so she could not identify any side effects that were not listed in the leaflet from the national patient support group. The complainant submitted that the German leaflet implied that she was illegally administered a medicine that was not licensed for use in the UK and was intended for only countries in which the side effects were explained. The complainant raised the matter with both her consultant and with Amgen in 2012 and received no acknowledgement from Amgen.

The complainant stated that within 3-6 weeks, she experienced unexpected side effects, not listed in pre-treatment information supplied by Amgen, in that she had cracks at the side of her mouth and severe mouth and tongue ulcers. The complainant contacted the national patient support group which told her that this was a side effect of Prolia and that the medicine had a yellow card marker. The complainant submitted that she was never told that Prolia was still on trial and that she had not been given enough information upon which to make an informed decision to start treatment.

The complainant and her consultant had both contacted Amgen in 2013 but the complainant submitted that the company was not helpful. Amgen denied all knowledge of mouth ulceration and only referred to osteonecrosis of the jaw. The booklet provided by Amgen after Prolia had been administered clearly listed non-healing sores of the mouth as a 'rare side effect'.

The complainant considered that, without her knowledge, she had been included in a trial. If she had known that Prolia had a 'yellow marker' she would not have agreed to treatment.

The complainant submitted further information and copies of correspondence between her consultant and Amgen and alleged that Amgen appeared to be withholding details of mouth ulceration in the UK in order to obtain a licence for Prolia. The company appeared to state that it did not need to list all side effects under UK regulations and so the information had been withheld. In the complainant's view Amgen appeared to be ignoring its 'duty of care' to all patients. The complainant noted that mouth ulceration was referred to in information given to patients in other countries and she requested a full investigation into the conditions relating to the use of Prolia in the UK.

The detailed responses from GlaxoSmithKline and Amgen are given below.

The Panel noted that the complainant was a patient who considered that she had experienced an adverse event as a result of the administration of Prolia. The Panel noted that invariably such individuals were only moved to complain when they felt strongly about a matter. The Panel noted that whilst the complainant raised a number of matters it could only consider those which fell within the scope of the Code. Patient safety was extremely important. It was not clear whether the patient had reported the side effect under the yellow card scheme but she had discussed the matter with various health professionals and been in contact with Amgen. The relevant procedures at Amgen should have ensured that the data was dealt with appropriately.

The Panel noted the relationship between Amgen and GlaxoSmithKline in relation to the promotion of Prolia. It further noted GlaxoSmithKline's submission that its role was limited to the patient support booklet and the Panel considered that aspect of the complaint in relation to both companies.

In the complaint against Amgen the complainant's general concern was about the alleged failure to provide information about side effects prior to the administration of Prolia and the failure to provide appropriate information in subsequent correspondence.

The Panel noted that the complainant's physician was responsible for her clinical care and associated matters. Pharmaceutical companies were only responsible under the Code for matters which came within its scope including the provision of material for patients. Amgen had provided information to the complainant and to the complainant's physician.

The Panel noted Amgen's submission that it had not been involved in any patient materials used by the national patient support group.

The Panel noted the complainant's concern that she had been provided with a foreign language patient leaflet after the medicine had been administered.

The Panel noted Amgen's explanation; the Prolia box had two patient leaflets, one in German and one in English. The health professional who administered the product read the English version, handing the unopened German version to the complainant. According to Amgen the hospital had apologised to the complainant about this matter. That the health professional had failed to give the complainant the English leaflet provided was not Amgen's responsibility under the Code. The Panel considered that this matter was most unfortunate and had caused the complainant distress. Nonetheless, the Panel considered that both the content of non-promotional package leaflets and the provision of the wrong version to the complainant were not matters that Amgen was responsible for under the Code. The Panel ruled no breach of the Code as both matters were outside the scope of the Code.

The complainant appeared to be under the misapprehension that she was on a clinical trial sponsored by Amgen. That was not so. Amgen submitted that it had not supported any trials at the hospital and the complainant's physician had confirmed that the administration of Prolia was not part of any trial. The product had a marketing authorization. It appeared from the complaint that this misunderstanding might have arisen when the complainant was advised by a patient organisation that there was a 'yellow card marker on Prolia' by which the Panel assumed that the complainant was referring to the Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card scheme for reporting suspected adverse events. The Panel noted that the yellow card scheme applied to, *inter alia*, all medicines and vaccines irrespective of how long they had been on the market. The Panel noted Amgen's submission that all Prolia promotional materials included the required statement regarding how adverse events should be reported. The Panel noted that the complainant bore the burden of proving her complaint on the balance of probabilities. No promotional materials for Prolia had been provided by the complainant. The Panel therefore ruled no breach of the Code.

The Panel noted that the complainant might have been referring to the inverted black triangle symbol which when required by the licensing authority on promotional material denoted that special reporting was required in relation to adverse events. The Panel noted Amgen's submission that whilst Prolia was subject to special reporting all promotional material displayed the inverted black triangle symbol. The Panel noted that the European Medicines Agency (EMA) removed the black triangle reporting requirements for Prolia on 25 April 2013 and therefore this requirement no longer applied. In any event the requirements in the Code did not apply to patient materials. The Panel noted its comment above about the burden of proof. No promotional materials had been provided. No breach of the Code was ruled which was upheld on appeal by the complainant.

The Panel then considered the allegations about information on side effects in relation to the package leaflet provided by the complainant and the letter from Amgen to the complainant. The Panel noted the complainant's comments about worldwide differences regarding adverse events. The Panel noted that all companies, including Amgen, had to comply with the local regulatory requirements which differed globally. The Panel noted Amgen's submission that the EU determined whether an adverse event should be listed in an SPC based, *inter alia*, on the likelihood of a causal relationship. That an adverse event was listed in the SPC or its equivalent in one country did not automatically mean that it should be listed in those of other countries. The contents of SPCs were a matter for the regulators. The Panel noted that the patient leaflet dated March 2012 listed as a rare side effect 'persistent pain and/or non-healing sores of the mouth or jaw'. The SPC listed osteonecrosis of the jaw as a rare adverse event. Details were also given in Section 4.4 Special warnings and precautions for use.

The Panel noted the correspondence sent by Amgen to the complainant and did not consider that it was misleading or otherwise an unfair reflection of the SPC with regard to adverse events and the complainant's experience with mouth ulceration and suspected lichen planus. The Panel ruled no breaches of the Code. Two of those rulings were appealed by the complainant but upheld by the Appeal Board. The complainant also alleged a breach that when promotional material referred to published materials, clear references must be given. The Panel noted that no promotional material for Prolia has been provided by the complainant. No breach of the Code was ruled, which was upheld on appeal by the complainant.

The Panel noted its comments and rulings above. It was most unfortunate that the complainant was concerned about Amgen's conduct. However, the Panel did not consider that Amgen had failed to maintain a high standard of conduct. The company had written to the complainant and to her physician to explain the position. The Panel ruled no breach of the Code and subsequently no breach of Clause 2, which were upheld on appeal by the complainant.

In the complaint against Amgen and GlaxoSmithKline the Panel examined the leaflet provided by the complainant. According to Amgen, the patient leaflet provided by the complainant was part of its support programme for patients who had been prescribed Prolia.

The Panel noted that the booklet 'Understanding Osteoporosis' had been sponsored by both Amgen and GlaxoSmithKline as part of its Prolong Patient Support programme. The booklet discussed the Prolong programme, managing osteoporosis; exercising and continued to maintain strong bones and possible side-effects. The section on side-effects listed 'Common side effects', 'Uncommon side effects' and 'Rare side effects'. Rare side-effects (affected 1 to 10 users in 10,000) included persistent pain and/or non-healing sores of the mouth or jaw. The list of side effects was followed by 'If any side effects get serious or if you notice any side effects not listed here, tell your doctor or pharmacist' and 'See Package Insert Leaflet for further information'.

The Panel noted Amgen's submission that the reference in this booklet to persistent pain and/or non-healing sores of the mouth or jaw was intended to describe the rare adverse event of osteonecrosis of the jaw in patient friendly language. In this regard, the Panel considered that the patient booklet was a fair reflection of the UK SPC and ruled no breach of the Code.

The Panel noted its ruling above and considered that neither Amgen nor GlaxoSmithKline had failed to maintain high standards nor that a ruling of a breach of Clause 2 was warranted. No breaches of the Code including Clause 2 were ruled.

A patient who had been prescribed Prolia (denusumab) complained about the information which Amgen UK Limited had supplied about the medicine. Prolia was indicated, *inter alia*, for the treatment of osteoporosis in postmenopausal women at increased risk of fractures. The matter was subsequently taken up with GlaxoSmithKline UK Limited which co-promoted Prolia.

COMPLAINT

The complainant explained that in August 2012, she was injected with Prolia at a local hospital but before agreeing to treatment she made thorough enquiries at the metabolic bone clinic and was told that the only side effects were listed in the leaflet issued by the national patient support group, which were inaccurate and incorrect (a copy of the leaflet was provided).

The complainant stated that she was also given a leaflet which was not written in English, so she could not identify any further side effects not listed in the leaflet from a national patient support group. The consultant wrote a note to this effect on a form which she completed to Amgen and did not receive any acknowledgement when she complained of this fact. she also raised this issue with her consultant at the clinic and gave him the leaflet she had been handed after the injection. The complainant read the leaflet and agreed that it was not printed in English. The complainant's consultant stated he/she would address this with Amgen.

The complainant stated that within three to six weeks, she began suffering side effects that were not listed on the osteoporosis information supplied by Amgen after commencing treatment; by that time she had cracks at the side of her mouth, severe ulceration in her mouth and tongue for no apparent reason other than the use of Prolia, but was unable to find any relief from the medical profession. In desperation the complainant rang the patients help line at the national patient support group and was informed that this was a side effect of Prolia together with other side effects not listed on information given to patients before treatment. The complainant stated that she was also told that there was a yellow card marker on Prolia. The complainant submitted that at no time was she told that Prolia was still under trials; was not given an opportunity to make an informed decision and was therefore not aware of the hazard likely to occur after the administration of Prolia.

The complainant stated that she asked her consultant to write to Amgen to ascertain what the symptoms of other patients were (who had also reported the same side effects as her). The complainant did not have a copy of her consultant's letter to Amgen but she did have a copy of Amgen's not very satisfactory, reply: her consultant agreed that the complainant could contact Amgen which she did in August 2013.

In October 2013 the complainant received an acknowledgement from Amgen (copy provided). In its reply to her consultant, Amgen appeared to deny all knowledge of this ulceration and only referred to ONCJ (osteonecrosis of the jaw) which was mentioned in the osteoporosis leaflet. The booklet provided by Amgen after Prolia had been administered, clearly listed non-healing sores in the mouth as a 'rare side effect'. These statements were ambiguous and Amgen would appear to be trying to conceal the truth (the complainant provided a copy of her letter to Amgen).

The complainant had received another letter from Amgen (dated 14/10/13, copy provided) which claimed exemptions under the Code. In the complainant's view this showed further casual dismissal of patients' complaints, when Amgen urged patients to contact it direct should the need arise. This fell far short of any reassurance Amgen gave in promising to assist in answering complaints.

The complainant alleged that Amgen treated patients who attempted to contact it with disdain and the company obviously needed to try and conceal its mistakes by adopting such a contemptuous attitude. Amgen treated patients like 'laboratory rats' by not being honest about the side effects before treatment and the fact that Prolia was still subject to a 'yellow marker'.

The complainant noted that Amgen had advised her to speak to her consultant which she had done, and he/she was unable to help. This was why, with her consultant's approval, the complainant had contacted Amgen for an explanation.

The complainant considered that she had been co-opted onto a trial of which she was unaware. If she had known that there was a 'yellow marker' on Prolia, she would not have agreed to treatment. The complainant submitted that she was unable to make an informed decision without this information.

The complainant submitted that the administration of Prolia had had dire consequences upon her daily life and her quality of life. It was a long hard battle to try and obtain treatment to assist in the relief of the very painful symptoms as the result of Prolia being used. The complainant was still receiving treatment from a local dental hospital in an attempt to alleviate her suffering and had undergone a biopsy on her tongue to ascertain that it was not carcinogenic.

The complainant submitted that all she had been told was that Prolia had affected the auto immune system. Amgen did not make clear the dire consequences this medicine had upon the quality of patients' lives. It even denied there was a problem (other than

osteonecrosis of the jaw (ONCJ). The side effects were listed but patients were only given that information after the treatment had been administered, although Amgen denied their existence in its letter to her consultant.

The complainant stated that surely patients treated with a 'yellow marker' medicine should be told that it was still under trial. Amgen appeared to be trying to deceive patients and co-opt them to submit to treatment without all the correct information to participate in a medicines trial.

The complainant stated that without all the correct, relevant information patients could not make an informed decision as to the possible long term effects the medicines might have on their health and indeed their everyday quality of life. The complainant's attempts to gather the correct information on Prolia had met with obfuscation, denials and refusal to address the issue raised. This situation was completely unacceptable and Amgen should be held to account for the poor dissemination of information on its product and its effects on unsuspecting patients.

The complainant referred to Clause 7.9 of the Code.

When writing to Amgen, the Authority asked it to consider the requirements of Clauses 2, 4.10, 4.11, 9.1 and 22.2 of the Code in addition to Clause 7.9 as cited by the complainant.

Case AUTH/2645/10/13

RESPONSE

Amgen expressed its sympathies to the complainant for the unpleasant symptoms she described in the weeks following her Prolia injection, and its disappointment that its actions to date concerning her case had fallen short of her expectations and resulted in a formal complaint.

Amgen stated that it strongly considered that it had not failed to maintain the justifiably high standards expected by the regulatory authorities, the Association of the British Pharmaceutical Industry (ABPI), health professionals, patients and indeed the company itself. Amgen took all matters affecting patient safety extremely seriously and was keen to swiftly conclude this case to the satisfaction of all concerned.

In particular with reference to the complainant's serious assertion that the company had in some way denied knowledge of adverse effects related to Prolia or had attempted to 'conceal mistakes', Amgen categorically stated that this was not the case. Amgen had a rigorous approach to the collection and assimilation of adverse event data in accordance with EU regulations and updated the summary of product characteristics (SPC) and package leaflet when required based on the emergence of new safety risks.

Amgen stated that it had thoroughly reviewed its current and historical clinical development programme for Prolia and had not found any Amgen-supported Prolia trials carried out at the hospital where the complainant was treated. Thus, to Amgen's knowledge, the complainant had never been enrolled in an Amgen-supported Prolia trial. The complainant's consultant, the prescribing physician, confirmed in October that the administration of Prolia to the complainant was not part of any kind of trial.

Amgen stated that it had not been involved in the supply, creation or authorship of any patient materials used by the national patient support group. The only materials it had supplied to the society had been a press release before the launch of Prolia in the UK (May 2010) and the summary report of 'breaking point', an overview of the state of osteoporosis in the UK (May 2011).

Regarding the foreign leaflet given to the complainant Amgen stated that the hospital had confirmed that the Prolia box which contained the dose given to the complainant contained two patient information leaflets, one in English and in German (all Prolia boxes contained two leaflets of which one was in English). The nurse who administered the dose read the English leaflet before giving the injection, and handed the other unopened leaflet to the complainant, not knowing that this second leaflet was not in English. Unfortunately the complainant thus only saw the German version of the patient leaflet. Amgen noted that the hospital had submitted that it had apologised to the complainant on several occasions regarding this incident.

Amgen explained that Prolia was included in the UK 'Black Triangle' product list and had therefore been subject to intense monitoring since it was launched in June 2010.

With the introduction of the new EU-wide additional monitoring scheme, the European Medicines Agency (EMA) determined that Prolia did not meet the criteria for a black triangle product. Consequently, the EMA removed the black triangle reporting requirements for Prolia on the 25 April 2013 when it released the first EU-wide list of medicines subject to additional monitoring.

In accordance with the requirements of Clause 4.10, all Prolia promotional materials included the required statement regarding how adverse events should be reported.

Amgen stated that whilst Prolia was subject to special reporting, as required by Clause 4.11 of the ABPI Code, all promotional material displayed the inverted black triangle symbol.

Amgen stated that when patients participated in trials of its products, information was provided to the investigators on all aspects of the medicine being researched and full informed consent was always obtained from patients prior to their inclusion. However, as stated above, the complainant's treatment was not part of a clinical trial.

Amgen stated that it had not established a causal relationship between Prolia and mouth ulceration

and consequently mouth ulceration was not an identified risk with the medicine.

Amgen constantly monitored all reported adverse events, which were analysed and assessed for any new potential safety risks. When such safety risks were identified, the competent authorities were informed (ie MHRA, EMA etc) and following those discussions, the SPC and other related materials were amended appropriately based on this evidence. This process formed a critical part of Amgen's commitment to comply with Clause 7.9.

Amgen recognised that 'persistent pain and/or non-healing sores of the mouth or jaw' was listed as a rare side effect of Prolia in the patient information leaflet. That description was intended to describe the rare adverse effect of osteonecrosis of the jaw (listed in the SPC) in patient friendly language appropriate for a patient leaflet. Osteonecrosis of the jaw was a rare but recognised adverse effect of anti-resorptive medicines (including Prolia), which could manifest as deep, non-healing mouth sores leading eventually to exposed mandibular or maxillary bone.

Amgen was pleased that the complainant had received expert dental assessment following the persistence of her symptoms. The company could not comment on the complainant's clinical care since her symptoms emerged but it appeared that appropriate steps had been taken to rule out osteonecrosis of the jaw.

Mouth ulceration (or lichen planus), as experienced by the complainant had not, to date, been identified as adverse events with a direct causal association to Prolia and therefore did not appear as established or 'expected' adverse effects in the SPC.

Amgen knew that the Canadian product monograph for Prolia specifically mentioned tongue ulceration and lichen planus as having occurred in less than 1% of patients in the large-scale, phase 3 Prolia trial. Canadian authorities required all adverse events from the trial to be recorded in this monograph regardless of whether they were recognised Prolia-related adverse effects or events that had arisen unexpectedly at some point following Prolia administration. Current EU legislation did not require all adverse events to be listed at such length. Rather, the SPC presented the recognized adverse effects of a medicine identified via thorough assessment of safety data.

In summary, the analysis of safety reports to date had not established mouth ulceration or lichen planus as a recognised adverse effect related to Prolia use. The Prolia SPC had thus not been updated with regard to mouth ulceration and there were no current plans for a future update to include this as a specific side effect. However, should such safety risks appear in future Amgen would take all appropriate steps to amend Prolia materials accordingly to ensure paramount commitment to patient safety was maintained.

Amgen stated that as a pharmaceutical company which operated in accordance with the Code, its direct involvement with patients was limited. A patient support programme was one way by which additional education and support could be provided to patients and in that regard the company provided a patient support programme, PROLONG, to patients via their treating clinician. This programme provided further information on their postmenopausal osteoporosis, related conditions and lifestyle changes, as well background information on Prolia. The PROLONG programme operated in accordance with ABPI guidance outlined in 'Guidance notes for patient safety and pharmacovigilance in patient support programmes'. The programme was entirely voluntary and to ensure patients were not influenced inappropriately on what treatment they should receive, they could not enrol unless they had already been prescribed Prolia. Once enrolled, patients then directly received the information that the programme offered. Given that the copies of patient material provided by the complainant displayed the PROLONG logo across the top border, Amgen assumed that she was enrolled on this programme by her clinician. Amgen submitted that the PROLONG patient support programme provided a valuable resource to any patient prescribed Prolia and demonstrated the company's commitment to patients by providing education and support to help ensure they got the most out of its medicines.

Amgen stated that it considered that it had upheld its requirements in adverse event reporting, risk management follow up and appropriate responses to health professionals and the public in accordance with the Code. For example, regarding medical information responses, in this case the following process was followed: Amgen replied to enquiries about Prolia in accordance with the Code (Clause 22.3) and The Pharmaceutical Information and Pharmacovigilance Association (PIPA) guidelines. Medical information received a request for information directly from the complainant on 27 August 2013. In accordance with the Code (Clause 22.3), Amgen informed the complainant that she should discuss any personal medical matters with her treating physician. Simultaneously, Amgen contacted the treating physician to tell him about the complainant's concerns so that the matter could be appropriately discussed between the two.

Amgen considered that it had complied with the Code, both in general and specifically in relation to the clauses cited by the Authority, including Clause 2. Amgen again offered its sympathies to the complainant for the symptoms she had endured and for her dissatisfaction with Prolia and Amgen to date. Amgen hoped the above information reassured the complainant of the appropriateness of the company's conduct and how seriously and carefully it considered all matters of patient safety. Amgen would continue to rigorously monitor all adverse event data generated by the use of its medicines and take appropriate action should new risks be identified.

* * * * *

On receipt of Amgen's response it was noted that Prolia was co-promoted with GlaxoSmithKline UK Limited. Some of the enclosures provided by Amgen included the names of both companies

and so the matter was additionally taken up with GlaxoSmithKline. When writing to GlaxoSmithKline the Authority asked it to consider the requirements of Clauses 2, 4.10, 4.11, 9.1 and 22.2 of the Code in addition to Clause 7.9 as cited by the complainant.

RESPONSE

GlaxoSmithKline explained that Amgen Europe was the marketing authorization holder for Prolia and GlaxoSmithKline co-promoted. GlaxoSmithKline stated that it agreed with Amgen's response above and explained that its only involvement in this matter was limited to one of the documents referred to by the complainant which featured both companies' logos. This was an item intended for patients as part of the PROLONG patient support programme, and was received by the patient after the treating clinician has prescribed Prolia and enrolled her in the scheme. GlaxoSmithKline noted that the information on side effects highlighted in this item was consistent with the patient information leaflet at that time.

* * * * *

Shortly after writing to both companies, the Authority received further information from the complainant.

FURTHER INFORMATION FROM THE COMPLAINANT

The complainant stated that her consultant had forwarded her the reply from Amgen dated 14 October 2013. The complainant stated that she found the contents of the letter alarming and extremely distressing.

The complainant stated that the letter was in direct contravention to the reply sent previously by Amgen where it stated that ONCJ was the only mouth problem created from use on patients of Prolia, which was proved to be an errant deception. Reading the reply, the complainant alleged that Amgen appeared to be withholding the details of the mouth ulceration side effect in the UK in order to obtain a licence to issue the medicine. The company had failed to inform patients that Prolia was still under trial. Surely this company had a duty of care to patients, no matter in which country they resided?

The complainant stated that Amgen gave reasons in its opinion which allowed it to use Prolia without revealing side effects. The company's interpretation appeared to be that it was not legally required to list all side effects under UK regulations, so it had chosen to withhold this information, despite the fact that numerous cases had been reported in other countries. This was an errant disregard of its responsibilities of a duty of care. The complainant stated that this was clearly covered in Clauses 7.2, 7.6 and 7.9. As it was, patients were informed of possible side effects after receiving Prolia.

Further, with reference to Amgen's letter, the complainant reiterated that the leaflet she was given was not written in English which implied that a medicine not licensed for use in the UK was administered illegally to her. Obviously the particular batch administered to her was destined for only the countries in which the side effects were explained. The complainant queried whether Prolia was legally administered to her. This further supported her comments that British patients were being used as part of an experiment. All patients should be informed that the medicine was under trial where ever they resided.

The complainant stated that there were obviously complex conflicts of interests which avoided the issues being raised. The complainant alleged that certain relevant and important information was being withheld which showed a lack of concern and patient care. In the complainant's view, Amgen appeared to be ignoring its 'duty of care' to all patients.

The complainant submitted that she had endured 15 months of agony and discomfort; as she could not eat properly she sometimes had to drink warm drinks through a straw. The complainant stated that she had to follow a very bland diet and had also endured a lot of distress with pain, discomfort and loss of sleep.

The complainant stated that as Amgen had withheld full information on Prolia's possible side effects, none of the medical practitioners consulted knew that her symptoms were related to the administration of Prolia. As a result, the complainant had had to consult numerous professionals in an attempt to diagnose the problem. A professor at the local dental hospital helped to relieve the symptoms, as did her own GP. The complainant stated that she needed to know how long this discomfort would continue. Could Amgen offer a cure as it was responsible?!

The complainant considered that the national patient support group needed to be commended for giving her this very important information, no one else was either able or willing to admit that ulceration was a side effect.

The complainant found that the most upsetting and distressing aspect was that, in full knowledge that the fact she had reported were true, Amgen denied that it existed. It was also compounded by the fact that Amgen chose not to inform any UK patient.

The complainant objected to being deceived by Amgen, which appeared to do an excellent job of treating UK citizens as second class. This of course did very little for customer relations.

The complainant was unable to respond to Amgen's letter to her consultant as Amgen had made it quite clear that it was not prepared to discuss any concerns or issues with the patient being used in its trials.

Urgent amendments were required to inform all patients of the serious consequences which could arise from the use of Prolia, also that Prolia was still under trial before they submitted to treatment.

Amgen was failing patients and failing to adhere to its legal obligations in the care of patients. What Amgen had done was evil and cruel in marketing Prolia knowing that it could cause the terrible suffering. The complainant stated that it was still causing severe and debilitating side effects which impacted upon the quality of her and her family's life, and which would continue for some considerable time. Being used in this manner by Amgen had had severe effects upon her mental and physical well being.

The complainant was extremely concerned that Amgen considered that it was allowed to market Prolia in the UK without giving full information on possible side effects. Even worse, patients were not informed that Prolia was still under trial. The complainant understood that this information was available to patients in other countries and requested a full investigation into the conditions relating to the release of Prolia in the UK.

The complainant noted Amgen's statement that mouth ulceration had been reported as a rare side effect of Prolia. However, as patients and clinicians were not informed of this possible side effect, it might have occurred without being connected to the use of the medicine particularly as it might be used on people less able to associate their condition with the use of the medicine due to age, ill health or infirmity. In the complainant's case, it had taken visits to a number of medical professionals as well as invasive tests to establish the likely cause of her symptoms. All of this would not have been necessary had she been informed of the possibility beforehand, or at least been given some guidance after the event, rather than receiving flat denials from Amgen.

Amgen had created an international demarcation line of what it considered relevant to the majority of regulations covering the care of UK patients and a lack of consideration for patients' welfare. No-one, whatever their nationality, colour or creed should be treated in this manner - pain and discomfort were universal, no-one was impervious to it.

Case AUTH/2645/10/13

FURTHER RESPONSE FROM AMGEN

Amgen noted the complainant's allegation that its letter to the complainant's consultant was inconsistent with the reply given by the nurse that treated the complainant.

- Amgen's letter to the complainant's nurse, 11 June 2013, was in response to specific questions about the frequency of mouth ulcers and details of the company's experience of such symptoms in association with Prolia. Amgen researched the EU and US prescribing information for Prolia and informed the nurse that there was limited information regarding mouth ulceration following use of Prolia. In circumstances where the national patient support group had notified the nurse that treated the complainant of some reports of mouth ulceration from Canada, Amgen tried unsuccessfully to research this issue.
- Amgen's letter (14 October 2013) was in response to a request from the complainant's consultant, about the difference between the Canadian and UK prescribing information for Prolia, and explained that the product information for a medicine might be slightly different in different territories as a result of compliance with the requirements of the various regulatory authorities.

Amgen submitted that there was no contradiction and both letters stated that mouth ulceration was not an expected side effect as per the UK SPC. The two letters were sent from and directed to different individuals and covered different issues: the letter to the nurse who treated the complainant identified the research done by Amgen and stated that it had been unable to research the Canadian reports mentioned by the national patient support group; and the letter to the complainant's consultant dealt with differences between the UK and Canadian prescribing information for Prolia.

The content of an SPC and a patient information leaflet was determined by local and regional regulatory requirements and assessments undertaken by the relevant regulatory authorities. It was therefore inevitable that the product information approved by a regulatory authority and put into circulation in one territory would not be the same in all respects as that approved by a different regulatory authority in another territory. Amgen noted that the product information in the Prolia SPC and patient information leaflet used in the UK, per the centralised procedure, was the same as that used throughout the EU.

Amgen submitted that the position with respect to the inclusion of information about potential adverse reactions associated with the use of a medicine was particularly complex. In some countries, such as Canada, all possible adverse reactions (where a health professional had concluded that a causative relationship might be present) were included in the comprehensive product monograph (the equivalent of the SPC in Europe). Consequently, numerous potential adverse events reported from clinical trials were listed, even where it was not known whether the trial participant actually received the product in question or placebo. The EU determined whether an adverse event should be listed in the SPC based on a range of factors including the severity of the reaction, the numbers of reports and the likelihood of a causative relationship with use of the medicine. The provision of long lists of possible adverse reactions, without thorough assessment of their association with the medicine in the context of all the accumulated safety data, might not help prescribers and patients and might detract from other important information.
The product information contained in the SPC and patient information leaflet for Prolia (including the warnings of potential adverse reactions) was fully approved by the competent regulatory authorities as properly reflecting the available scientific data, before being put into circulation.

Amgen took the proper investigation and assessment of potential adverse reactions very seriously. Individual reports of adverse events, like

those of the complainant, received by Amgen were captured on the global safety database and reported to the regulatory authorities as required by law. Additionally, scientists and physicians at Amgen regularly reviewed all reports on the database to determine if there was any evidence to indicate a new safety risk with a product. Individual cases were medically reviewed together with information in the scientific literature and, as explained above, if the evidence suggested a risk the company would liaise with the regulatory authorities to suggest amendment to the product information. In parallel, the EU regulatory authorities, independently of the licence holding company, also monitored safety data and required SPC amendments when they concluded they were justified.

Amgen was, for obvious reasons, unable to advise in relation to the complainant's particular condition or to provide information on the likely duration of her symptoms. Cases of mouth ulcer had been reported only very infrequently in association with use of Prolia and the evidence to date was not sufficient to reach a conclusion about a causative relationship or to require the SPC to be changed. Amgen submitted that there were many causes of mouth ulceration, unrelated to Prolia and in these circumstances it would be inappropriate for Amgen to comment on the likely outcome in the complainant's case.

In summary, while Amgen understood the complainant's frustration, the evidence available to Amgen had not indicated that a warning in relation to mouth ulceration in association with Prolia was appropriate. The company would, of course, review its product information in the context of all reports of adverse events including the symptoms experienced by the complainant.

Amgen noted the complainant's belief that she was unknowingly included in a Prolia clinical trial. Amgen reiterated that, to its knowledge, the complainant had never been enrolled in an Amgen supported Prolia trial.

The complainant also suggested that the Prolia administered to her might not have been licensed for use in the UK, given that the leaflet provided to her was not in English. Amgen had addressed this issue above, based on the information provided to it by the nurse that treated the complainant, although the source of the product administered to the complainant was a matter for the local hospital, rather than for Amgen.

Amgen considered that it had fully answered all of the questions relating to Clauses 2, 4.10, 4.11, 7.9, 9.1 and 22.2. In particular, it considered that it had complied with all requirements with respect to appropriate responses to the consultant, nurse and the complainant in accordance with the Code.

Finally, Amgen again expressed its sympathy to the complainant in relation to the unpleasant symptoms and distress that she had experienced.

Case AUTH/2647/10/13

FURTHER RESPONSE FROM GLAXOSMITHKLINE

GlaxoSmithKline reiterated that Amgen Europe held the marketing authorization for Prolia and that GlaxoSmithKline co-promoted it; GlaxoSmithKline's involvement was limited to certification of the Prolong booklet.

GlaxoSmithKline considered that the complainant's further comments were addressed towards Amgen – as such it considered it had no further involvement in the matter; Amgen agreed with this position.

GlaxoSmithKline expressed its sympathies to the complainant for the symptoms that she had endured

PANEL RULING

The Panel noted that the complainant was a patient who considered that she had experienced an adverse event as a result of the administration of Prolia. The Panel noted that invariably such individuals were only moved to complain when they felt strongly about a matter. The Panel noted that whilst the complainant raised a number of matters it could only consider those which fell within the scope of the Code. Patient safety was extremely important. It was not clear whether the patient had reported the side effect under the yellow card scheme but she had discussed the matter with various health professionals and been in contact with Amgen. The relevant procedures at Amgen should have ensured that the data was dealt with appropriately.

The Panel noted the relationship between Amgen and GlaxoSmithKline in relation to the promotion of Prolia. It further noted GlaxoSmithKline's submission that its role was limited to the Prolong booklet and the Panel considered that aspect of the complaint in relation to both companies.

Case AUTH/2645/10/13

The complainant's general concern was about the alleged failure to provide information about side effects prior to the administration of Prolia and the failure to provide appropriate information in subsequent correspondence.

The Panel noted that the complainant's physician was responsible for her clinical care and associated matters. Pharmaceutical companies were only responsible under the Code for matters which came within its scope including the provision of material for patients. Clause 22 of the Code covered relations with the public and the patients. Clause 22.3 stated 'Requests from individual members of the public for advice on personal medical matters must be refused and the enquirer recommended to consult his or her own doctor or other prescriber or other health professional'.

The supplementary information referred to not intervening in the patient/doctor relationship and

referred to the need to take particular care with regard to enquiries about side-effects. Amgen had provided information to the complainant and to the complainant's physician.

The Panel noted Amgen's submission that it had not been involved in any patient materials used by the national patient support group.

The Panel noted the complainant's concern that she had been provided with a patient leaflet after the medicine had been administered. The package leaflet supplied was in a foreign language and the complainant had provided a copy. Clause 1.2 stated that the term 'promotion' did not include the labelling on medicines and accompanying package leaflets insofar as they were not promotional for the medicines concerned; the contents of labels and package leaflets were covered by regulations. Clause 1.2 also excluded SPCs from the definition of promotion.

The Panel noted Amgen's explanation; the Prolia box had two patient leaflets, one in German and one in English. The health professional who administered the product read the English version, handing the unopened German version to the complainant. According to Amgen the hospital had apologised to the complainant about this matter. The medicine package contained an English language version of the package leaflet which should have been provided to the complainant. That the health professional failed to do so was not Amgen's responsibility under the Code. The Panel considered that this matter was most unfortunate and had caused the complainant distress. Nonetheless, the Panel considered that both the content of non-promotional package leaflets and the provision of the wrong version to the complainant were not matters that Amgen was responsible for under the Code. The Panel ruled no breach of Clauses 22.2 and 9.1 as both matters were outside the scope of the Code.

The complainant appeared to be under the misapprehension that she was on a clinical trial sponsored by Amgen. That was not so. Amgen submitted that it had not found any Amgen supported trials at the hospital and the complainant's physician had confirmed that the administration of Prolia was not part of any trial. The product had a marketing authorization. It appeared from the complaint that this misunderstanding might have arisen when the complainant was advised by a patient organisation that there was a 'yellow card marker on Prolia'. The complainant alleged that Amgen was not being honest about the fact that Prolia was subject to a yellow marker. The Panel assumed that the complainant was talking about the yellow card scheme by which suspected adverse events could be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Panel noted that the yellow card scheme applied to, *inter alia*, all medicines and vaccines irrespective of how long they had been on the market. Clause 4.10 required all promotional material to include a prominent statement about reporting adverse events under the yellow card scheme. This requirement currently only applied to promotional materials.

The Panel noted Amgen's submission that all Prolia promotional materials included the required statement regarding how adverse events should be reported. The Panel noted that the complainant bore the burden of proving her complaint on the balance of probabilities. No promotional materials for Prolia had been provided by the complainant. The Panel therefore ruled no breach of Clause 4.10 in this regard.

During its consideration of this aspect the Panel noted that changes to the Code which were to come into effect on 1 May 2014 would require patient materials to include details of how to report side effects (Clause 23.3, 2014 Code).

The Panel noted that the complainant might have been referring to the inverted black triangle and Clause 4.11 which stated that when required by the licensing authority all promotional material must show an inverted black triangle to denote that special reporting was required in relation to adverse events. The Panel noted Amgen's submission that whilst Prolia was subject to special reporting all promotional material displayed the inverted black triangle symbol as required by Clause 4.11. The Panel noted that the European Medicines Agency (EMA) removed the black triangle reporting requirements for Prolia on 25 April 2013 and therefore this requirement no longer applied. In any event the requirements in Clause 4.11 did not apply to patient materials. The Panel noted its comment above about the burden of proof. No promotional materials had been provided. No breach of Clause 4.11 was ruled.

The Panel then considered the allegations about information on side effects in relation to the package leaflet provided by the complainant and the letter from Amgen to the complainant. The Panel noted the complainant's comments about worldwide differences regarding adverse events. The Panel noted that all companies, including Amgen, had to comply with the local regulatory requirements which differed globally. The Panel noted Amgen's submission that the EU determined whether an adverse event should be listed in an SPC based, *inter alia*, on the likelihood of a causal relationship with use of the medicine. That an adverse event was listed in the SPC or its equivalent in one country did not automatically mean that it should be listed in those of other countries. The contents of SPCs were a matter for the regulators. Clause 3 included a requirement that promotion was not inconsistent with the SPC and Clause 22.2 included a requirement that information for the public was factual and presented in a balanced way. The supplementary information listed the requirements of Clause 7 which also applied to information to the public. The Panel noted that the patient leaflet dated March 2012 listed as a rare side effect 'persistent pain and/or non-healing sores of the mouth or jaw'. The SPC listed osteonecrosis of the jaw as a rare adverse event. Details were also given in Section 4.4 Special warnings and precautions for use.

The Panel noted the correspondence sent by Amgen to the complainant and did not consider that it

was misleading or otherwise an unfair reflection of the SPC with regard to adverse events and the complainant's experience with mouth ulceration and suspected lichen planus. The Panel ruled no breach of Clauses 7.2, 7.9 and 22.2 on this point. The complainant also alleged a breach of Clause 7.6 which stated that when promotional material referred to published materials, clear references must be given. The Panel noted that no promotional material for Prolia had been provided by the complainant. No breach of Clause 7.6 was ruled.

The Panel noted its comments and rulings above. It was most unfortunate that the complainant was concerned about Amgen's conduct. However, the Panel did not consider that Amgen had failed to maintain a high standard of conduct. The company had written to the complainant and to her physician to explain the position. The Panel ruled no breach of Clause 9.1 and subsequently no breach of Clause 2.

Cases AUTH/2645/10/13 and AUTH/2647/10/13

The Panel examined the leaflet provided by the complainant. According to Amgen, the patient leaflet provided by the complainant was part of its support programme for patients who had been prescribed Prolia.

The Panel noted that the booklet 'Understanding Osteoporosis' (ref DMB-GBR-AMG-037-2012/UK/DNB 0002g/12/32043984) had been sponsored by both Amgen and GlaxoSmithKline as part of its Prolong Patient Support programme. The booklet discussed the Prolong programme, managing osteoporosis; exercising and continued to maintain strong bones and possible side-effects. The section on side-effects (page 18) listed 'Common side effects', 'Uncommon side effects' and 'Rare side effects'. Rare side-effects (affected 1 to 10 users in 10,000) included persistent pain and/or non-healing sores of the mouth or jaw. The list of side effects was followed by 'If any side effects get serious or if you notice any side effects not listed here, tell your doctor or pharmacist' and 'See Package Insert Leaflet for further information'.

The Panel noted Amgen's submission that the reference in this booklet to persistent pain and/or non-healing sores of the mouth or jaw was intended to describe the rare adverse event of osteonecrosis of the jaw in patient friendly language. In this regard, the Panel considered that the patient booklet was a fair reflection of the UK SPC and ruled no breach of Clause 22.2 of the Code.

The Panel noted its ruling above and considered that neither Amgen nor GlaxoSmithKline had failed to maintain high standards nor that a ruling of a breach of Clause 2 was warranted. No breach of Clauses 9.1 and 2 was ruled.

APPEAL FROM THE COMPLAINANT

The complainant stated that she suffered an adverse reaction immediately after receiving the injection in August 2012. Her blood pressure was elevated and she was admitted for observations.

The complainant stated that she was hospitalised as a result of an adverse reaction to Prolia and that Clause 7.9 had been breached. As this occurred in 2012 the 'black triangle' system was in force and was clearly displayed in the companies' documents and leaflets. The complainant alleged a further breach of Clause 7.9 in that Amgen did not make the full information available to prospective patients, only company promotional material. As a result patients could not make informed, constructive decisions as to their treatment. The recorded adverse effects must reflect the available evidence as stated in Clause 7.9.

The complainant stated that she had informed her consultant of her adverse reactions to Prolia in September 2012, additionally he/she was not even aware that she had been admitted to hospital after the injection! The complainant alleged that her consultant did not inform Amgen until one year after the event, despite the complainant asking him/her to do so at the time of the consultation. The complainant alleged that this again was in breach of regulations which stated that all adverse effects should be reported. This information in the case of UK residents appeared to be suppressed.

The complainant stated that Amgen had replied to her query one year after the regulations had changed. The complainant stated that her enquiry was initiated in 2012, when the black triangle marker was still in evidence.

The complainant alleged that Amgen still continued to dismiss a valid complaint which was initiated in 2012 and as such she alleged a breach of Clause 4.11, in that additional monitoring was required in relation to adverse reactions.

The complainant alleged that her complaint was reported within the timescale (2012) to the consultant in charge of her treatment at the time as per the company directives. The black marker regulations were clearly evident and required patients/consultants to submit adverse reactions.

The complainant stated that she did not receive a reply in 2012, and in 2013 she again raised this with her consultant; who agreed to contact Amgen, however it appeared that he/she delegated this task to the nurse that had treated her.

The complainant alleged that she was not informed at any time that there was a 'yellow marker' in force in 2012. This matter had not been addressed or explained by Amgen and was clearly in breach of the regulations.

The complainant alleged that she was not properly informed of adverse reactions until after receiving treatment. This information was apparently available to patients in other countries.

The complainant alleged that UK citizens were not being treated fairly, in breach of Clause 7.2. The evidence available to the company was not reflected in the material made available to patients, and leaflets were not sufficiently complete to enable patients to be able to form their own opinions.

The complainant alleged that there appeared to be no help or co-ordination to assist local medical practitioners, who were left with the problems of administering a new medicine and its consequent possible adverse reactions. Amgen appeared to have withheld information as to a medicine's adverse reactions and left its problems for the NHS to solve. Consultants appeared to have withheld information as to a medicine's adverse reactions from Amgen to the detriment of patients.

The complainant stated that the national patient support group was an accredited organisation. The complainant alleged that Amgen had compounded serious deceptions by the organisation and those who supported it. If the company was aware of these apparent errors, as stated, why did it not give the national patient support group the correct information? The complainant queried whether consultants who regularly lectured at the national patient support group meetings were giving the 'incorrect' information.

The complainant alleged that with regard to the statement by the nurse, she did not know that the Prolia pack contained two leaflets. This was brought to the complainant's attention by this complaint. The complainant had only spoken to this nurse on one occasion (in 2013) since the incident, in the presence of her consultant, and a witness who accompanied the complainant to this appointment because of ill-health. However, as a result of this incident the complainant had emailed the nurse (5/1/2014 copy provided) to ask for a copy of the English version, which he/she supplied. Presumably, this was the 2013 version and not the 2012 leaflet.

The complainant agreed that handing out incorrect literature was the responsibility of the hospital. The fact however did not cover what was or indeed what was not contained in the document.

The complainant noted that the legislation regarding the black triangle was still in operation in August 2012, when she received her initial treatment. The complainant had requested information about mouth sores and ulceration in September 2012. This complaint was confirmed to exist in 2013 by Amgen's letter so it was relevant to this case in 2012. The information was denied and this was clearly a breach of Clause 7.9. The complainant stated that she still suffered from severe sores and ulcerations of the mouth and the symptoms were not clearing and questioned if this was a precursor to ONCJ. The complainant considered that this adverse reaction was recognised and should be included in the company's literature. It appeared that further research by the company was required.

The complainant alleged that [Prolia] was subject to special reporting of adverse reactions (no matter how rare), when it was administered in 2012 and she was not informed. The complainant had a letter dated October 2012 from Amgen which confirmed her registration on the program (copy provided) and a further letter from Amgen, dated January 2014 to confirm that she had registered on the program so Amgen knew about her.

The complainant alleged that Amgen should exercise a moral conscience as it appeared to be unaware of this adverse reaction. There had been reports of [mouth] ulceration and non-healing mouth sores in the UK, USA and Canada from patients.

The complainant alleged that it was apparent that in other countries patients were at a loss as to who to turn for help, so it appeared that Amgen had failed international patients in addition to those in the UK (blog articles were provided).

The complainant alleged that the only additional information on Amgen's website was about skin infections which the complainant alleged she had also developed. At her consultant's instigation, the complainant was referred to a dermatologist and her consultant had a copy of this report.

The complainant alleged that the mouth ulceration and non-healing mouth sores appeared to be a common complaint of reported to the UK, USA and Canada. It would therefore be difficult and negligent for Amgen to ignore this as an adverse reaction, particularly as they could be a precursor to ONCJ. Amgen had a moral responsibility to patients to record all information, as Prolia was available worldwide. The complainant alleged a breach of Clause 7.9 as the available clinical evidence had not been disseminated to patients.

The complainant questioned why Amgen had reported the skin infections which were included on its recent updates but not include mouth ulceration and lichen planus as it had admitted that these existed. The complainant alleged a breach of Clause 7.2 as the material was not sufficiently complete for patients' information.

The complainant questioned why, from all the evidence in its possession from the UK, US and Canada that these adverse effects had occurred in patients, was it not included in Amgen's information to patients and prospective patients? Amgen appeared to be duty bound under Clause 7.2 and 7.9 to include this information. It was Amgen's responsibility to ensure the correct information was made available, even though it appeared to operate a 'selective' information pack for UK citizens.

The complainant questioned the statements by Amgen as from the information obtained from other countries, (blog articles were provided) its apparent lack of honesty left a lot to be desired.

The complainant questioned why Amgen appeared to dismiss the data amassed from other countries. Prolia was available worldwide and all patients were entitled to the same consideration whichever country they lived in. Cherry picking the regulations did not help the patients when they were suffering.

The complainant alleged that on all the literature supplied by Amgen, it recommended that all adverse effects should be reported. Although when this was done, Amgen did not appear to be able to offer any remedy to cure the suffering.

The complainant alleged that by admitting that Amgen was prepared to allow the national patient support group to proceed with the incorrect information, it had compounded a deception by not informing it. The national patient support group was the main distributor of all types of literature applicable to the treatment of osteoporosis and by not informing it of the correct information to convey to unsuspecting patients, this fell far short of its purported high standards.

The complainant was still concerned that her questions were not answered by Amgen in 2012 and this had still not been addressed or answered; the complainant queried whether this was because she was a UK resident.

The complainant alleged that when she received the treatment in August 2012, the black triangle system was still in existence for Prolia and therefore was relevant to her treatment and the adverse effects sustained.

The complainant questioned Amgen's statement in respect of the reporting of adverse effects as it would only receive comments from consultants. With the consequent result that this information was much delayed. The complainant considered that the reporting of adverse effects was over complicated and daunting for many people who suffered and the additional stress from this process was no doubt avoided by many people.

The complainant alleged that mouth ulceration and non-healing sores of the mouth had been admitted by Amgen earlier as a recognised adverse reaction; why did it deny it now? The complainant alleged a breach of Clause 7.9.

The complainant alleged that the admission that mouth ulceration and soreness of the mouth in the leaflet was very misleading to patients. Patients experienced these painful side-effects all over the world.

The complainant alleged that Amgen's explanation in the literature was a clear breach of Clause 7.2 and misled patients and should be remedied on its patient leaflets.

The complainant alleged that in relation to the company not accepting the adverse effect of mouth ulceration as a rare side-effect in the UK, why was it an admitted, reported fact in the US and Canada as per Amgen's letter?

Why had UK/EU patients, been let down by the regulations? The complainant alleged that the company was in breach of Clause 7.9.

The complainant agreed that she was enrolled in the program, indeed she received a further letter in January 2014, but the complainant did not find participation helpful as Amgen did not answer questions, participation was a two way process.

The complainant alleged that Amgen had replied to her enquiry in August 2013 about adverse effects initiated in 2012 when the black triangle system was in force, therefore Amgen's claim under the regulations did not apply.

The complainant alleged a breach of Clause 9.1 in that high standards had not been maintained.

The complainant alleged that Amgen had a moral responsibility to patients to record all information in their literature, as the medicine was available worldwide. The lack of clear unambiguous information was in breach of Clause 7.9.

The complainant queried why, if Amgen had included skin infections in its recently updated literature, it did not include mouth ulceration and lichen planus. The company had admitted that it did exist. This appeared to be a breach of Clause 7.2.

The complainant alleged that the admission by Amgen that mouth ulceration, soreness of the mouth and non-healing sores in its literature and the reference to ONCJ misled patients. Patients worldwide experienced these distressing adverse effects and the implication was that they might be a precursor to ONCJ. This particular paragraph in the company literature misled patients in breach of Clause 7.2.

The complainant stated that her experiences with Prolia and Amgen had been unpleasant and distressing. Not only had accurate information about the medicine not been supplied, the complaint alleged she also suffered a number of 'adverse reactions'.

The complainant alleged that both Amgen and GlaxoSmithKline were international pharmaceutical companies which picked and chose what information to release to patients about all of the adverse reactions patients could experience from the use of their products. The companies' biased responses were detrimental to patients' health and care.

The complainant alleged that the law in relation to the protection of UK citizens had clearly been breached from the lack of disclosure, by the companies' admission. In breaching these regulations, the companies openly admitted a selective policy as far as the release of all the information regarding adverse reactions to this medicine. Without UK regulation and codes of practice patients would be unable to voice their justified complaints and concerns regarding Prolia. The complainant submitted that from the documents recorded by other medical bodies (copies of which were provided), it was considered that insufficient evidence had been gathered to even commence its usage on patients, not only those in the UK. Reported adverse reactions included spontaneous fractures, cancer and problems with bone formation.

The complainant was puzzled as to why the thigh bone was now included in the DEXA scan, now she knew, since the information regarding 'spontaneous' fractures of both the thigh and jaw bone on tooth extraction had been published. This was yet another 'adverse reaction' not disclosed to patients. Patients

should be advised to check the internet for other countries' responses and reported adverse reactions.

The complainant stated that in her case, this would have proven invaluable, as Amgen openly admitted to letting the national patient support group continue to report inadequate literature, without informing them of all the relevant details. Withholding of this crucial information had proved detrimental to the complainant's and other patients' welfare.

The complainant alleged that Amgen's attitude was disconcerting and distressing; it still did not give an account of its actions, it appeared to only take what steps it could to avoid the very real complaints made regarding the adverse effect Prolia had on patients' lives, which the complainant found extremely unnerving.

The complainant stated that, having read other unbiased observations from medically qualified practitioners, which were more honest, she was terrified at the thought of what might happen in the future to her immune system as a result of being treated with Prolia.

The complainant now regretted placing her faith in the information handed out to UK citizens, as it could and probably would have far reaching deterioration on some patients involved in its usage.

The complainant stated that finally all UK members unwittingly participating in the use of Prolia would have to rely on the NHS to help them cope with their 'adverse reactions'. It was fortunate that such dedicated help and professionalism was available.

The complainant alleged that Amgen and GlaxoSmithKline would not be in the least concerned in the eventual fate of their participants. They had still not given a suitable explanation as to why they had not complied with the PMCPA regulations governing UK citizens' rights. Their actions had not been honest or unbiased in respect of the adverse reactions of Prolia.

The complainant stated that she still had an extremely sore mouth, ulceration and a severe skin infection and irritation, effects which had only recently been admitted by this company (web article provided).

The complainant stated that she was a UK citizen and entitled to the regulations quoted by the PMCPA as a right of protection, as other NHS bodies appeared, for some unknown reason, to allow Amgen to publish what it considered relevant. Internationally, this was an extremely irresponsible system to operate.

The complainant alleged that Amgen stated that it had 'no intention' of including this crippling, painful symptom (lichen planus) in UK 'adverse effects'. Surely it was within the PMCPA's remit to enforce and ensure that UK citizens had this knowledge before embarking, on a very destructive road to personal health and welfare, whilst also coping with the original deteriorating illness, for which this so called 'cure' was administered. The complainant hoped that the relevant steps would be taken to avoid other patients suffering unnecessarily as she had done and that in future truthful and unbiased information about Prolia would be freely available.

* * * * *

The complainant was asked to clarify her appeal in respect of which rulings of no breach of Clauses 9.1 and 2 she was appealing and to give reasons for appealing Clauses 2 and 7.6.

* * * * *

The complainant alleged that when she had received Prolia in 2012, it was still subject to the 'black triangle' until April 2013. Therefore all adverse effects should have been the subject of special reporting. The adverse effects the complainant started suffering were reported to her consultant in September 2012. The promotional material misled patients. Patients could not directly report adverse effects to the company. This fact was not clearly stated to patients and was ambiguous in breach of Clause 7.2.

The complainant noted that in 2012 Amgen was subject to special reporting of adverse effects in respect of the black triangle system. The complainant accepted that the promotional material of 2012 did display the black triangle and that Clause 4.10 was not breached.

The complainant alleged that in 2012 the information promoted by Amgen was not accurate, balanced or fair to patients, did not reflect the clinical evidence available to the company and was in breach of Clause 7.2. Patients had reported mouth ulcers and non-healing sores to the mouth in this country and worldwide.

The complainant alleged that Clause 7.9 had been breached by the company in 2012 as the information and claims in respect of side effects did not reflect the available evidence. Evidence was available from patients worldwide that the adverse effect of mouth ulceration and non-healing sores of the mouth had been reported (the complainant cited blog articles previously provided).

The complainant alleged that the material available to patients in 2012 was not sufficiently complete to enable patients to form their own opinion of the therapeutic value of the medicine, in breach of Clause 7.2.

The complainant alleged a breach of Clause 9.1 in that the high standards of the company had not been maintained. The material available to patients in 2012 was not of a sufficiently high standard due to the omissions of certain 'rare side effects' in its material despite evidence from patients worldwide. This could be prejudicial to patient safety and the complainant alleged a breach of Clause 2 in that the material promoted by the company in 2012 did not reflect the available clinical evidence.

The complainant alleged that Amgen had admitted that this adverse reaction had been reported by patients receiving Prolia, yet it stated it still did not intend to publish it. This action was in breach of Clauses 7.2, 2 and 9.1. The material promoted by Amgen was not accurate, fair or balanced in breach of Clause 7.2. As a result of this omission the material might have been prejudicial to patient safety, in breach of Clauses 2 and 9.1 as the high standards of the company had not been maintained.

The complainant noted that GlaxoSmithKline had stated it relinquished responsibility for publishing data. This was not clear in 2012 as both company logos were displayed. In view of GlaxoSmithKline's submission that Amgen was solely responsible for this information, the complainant had no alternative but to request that the appeal continued against Amgen.

The complainant alleged that Allergan knowingly passed inadequate information to other bodies, eg the national patient support group. The company had stated that information 'was taken from a general publication'.

The complainant alleged a breach of Clause 9.1 in that the company had failed to maintain high standards. The company had failed to disclose all of the available information to the national patient support group and patients.

The complainant noted that the material available to patients in 2012 referred only to Amgen and not GlaxoSmithKline. It was unclear whether both companies were involved when this complaint was initiated. GlaxoSmithKline had stated that it was Amgen's responsibility, which was now understood. By not releasing all of the relevant information, Amgen had influenced patient decisions. Not being fully aware of the dangerous, life changing, painful adverse reactions of mouth ulceration, and non-healing sores of the mouth. The company had openly admitted that it had prior knowledge of this adverse effect by stating that it occurred in some patients.

The complainant alleged that Prolia acted on the body's autoimmune system and the complainant categorically stated that she did not have mouth ulceration, non-healing sores of the mouth, skin infection or other painful conditions before she received Prolia.

The complainant alleged that Amgen had misled her and other patients by not revealing this particular adverse reaction, in breach of Clause 7.2. This information should have been released to the public to enable patients to form a balanced opinion. The company encouraged the use of the medicine by withholding this information from patients, in breach of Clause 7.2.

The complainant alleged that no information about the adverse reactions was given to the patient receiving this treatment until after the medicine was administered. Therefore the patient was unable to make an informed decision prior to receiving treatment.

The complainant alleged that this was in breach of Clause 7.2.

The complainant alleged that the detailed information provided in the form of statements of complaint from other patients (worldwide) supported her complaint of insufficient information being available to patients and withholding important adverse reactions on the material being made available to patients.

The complainant alleged that the clauses cited above had been breached and the company openly admitted that it would continue to do so in respect of patients in the UK. By failing to declare, upon request, the percentages of patients who experienced these and other adverse reactions, Amgen had perpetuated a deception. Amgen needed to comply with the Code. Was Amgen so large that it thought that it was exempt from the Code? Surely the Code was in place to protect UK citizens when they were being exploited and exposed to life changing and debilitating adverse reactions. If the Appeal Board did not enforce them - where did patients go?

The complainant alleged that Amgen had attempted to exonerate itself because she did not have sight of its leaflet. This would have been irrelevant as Amgen had admitted that this reported 'adverse reaction' was known, but it had chosen not to reveal it anyway to UK patients.

COMMENTS FROM AMGEN

Amgen noted that the complainant alleged that it had breached Clause 4.11 which required that when requested by the regulatory authority, all promotional material must display an inverted black triangle symbol to denote that special reporting/ additional monitoring of adverse reactions was required. Amgen submitted that as previously explained, promotional material for Prolia displayed the black triangle symbol during the period required by the regulatory authority and as such the company had complied with Clause 4.11.

Amgen noted that the complainant accepted that the promotional material of 2012 displayed the black triangle. However, the complainant appeared to suggest that because Prolia was subject to special reporting as indicated by the black triangle and a 'yellow marker' when she reported mouth ulceration, the company's handling of her adverse event report had been inadequate. This was not so. Amgen provided information on the additional monitoring/ special reporting requirements and the Yellow Card Scheme for the benefit of the complainant.

Amgen submitted that whilst not a consideration under Clause 4.11, all adverse events that were reported to it, irrespective of which product was suspected of being linked to the adverse event, whether the report was made by a health professional or patient and whether the product was subject to special reporting or not, were processed in the same way through its case management system and reported as required to the relevant regulatory authorities.

Amgen noted that the complainant had made various allegations concerning its provision of information relating to Prolia. Specifically, that in breach of Clause 7.2 and/or Clause 7.9:

- Amgen had not made available to prospective patients full information about side effects to enable patients to form their own opinions about the medicine and the information provided about side effects was selective and did not reflect the available evidence;

- The information concerning mouth ulceration and soreness of the mouth in the package information leaflet (PIL) for Prolia was misleading.

Pharmaceutical companies were not permitted to promote prescription only medicines to patients and as such the product information which the company made available to prospective patients in the EU was that contained in the product information designed for health professionals the SPC, and the information contained in the PIL. The promotion of medicines to health professionals was, however, permitted provided it complied with the law and the Code. The focus of Clause 7 of the Code was promotional information directed toward health professionals rather than information made available to the general public; nevertheless, Amgen had sought to address the complainant's concerns.

Amgen submitted that the content and format of information in the SPC and PIL for medicines marketed in Europe was prescribed by law and regulatory guidance and the information listed, including the warnings of potential adverse medicine reactions, was reviewed and approved by the regulatory authorities to ensure that it properly reflected the available scientific evidence, before the product was put into circulation. However, as described previously, the approach taken by the regulatory authorities to the content of SPC and the PIL - which reflected the SPC - was not consistent across the globe. Some countries, such as Canada, mandated that all possible adverse reactions reported during clinical trials were included in the product information. This was not the approach taken in the EU where inclusion of an undesirable effect in the SPC and PIL was based on the totality of a range of factors including the likelihood of a causal relationship with the relevant medicine, the severity of the reaction and the numbers of reports received. Accordingly, the fact that a company received one, or even several, reports of a suspected adverse reaction did not necessarily automatically translate into a warning for that adverse reaction in the SPC or PIL.

Amgen submitted that it had robust processes in place, as required by law, for signal detection and assessment ie processes to determine whether safety information it received was suggestive of a new side effect that should be included in product information and also patient leaflets. The company continuously monitored and evaluated the data available to it. If medical judgment and scientific interpretation of the available data suggested a risk, Amgen liaised with the relevant regulatory authorities to agree an amendment to the product information. In addition to the company review, in Europe, a similar process was also carried out by the regulatory authorities. Regulatory authorities reviewed both the individual reports of adverse reactions sent in by health professionals and patients and the comprehensive safety information reports which companies were required to submit on a periodic basis, so called, periodic safety update reports (PSURs) to determine if a change to the product information was required. PSURs were based on all available data and provided a critical analysis of the risk-benefit balance of the medicine taking into account new or emerging information about a medicine. In addition, the regulatory authority might compare the reporting frequency of a suspected adverse reaction with the expected frequency of the same adverse event in the general population. If the regulatory authority, based on its assessment of the available data, considered that product information should be amended, the company was required to implement the required changes as soon as possible.

Amgen submitted that product information and information for patients was continually updated throughout a product's life-cycle as the safety information reported to the company underwent the scrutiny described above. The safety profile of a product tended to emerge over time as larger and more diverse patient populations were exposed to the product following launch into the market. For example, the product information for Prolia was amended last year to add atypical femoral fracture as a side effect because this rare adverse reaction only became apparent two or so years after launch of the product.

Amgen submitted that contrary to the complainant's assertion, it never stated that it had 'no intention' of including lichen planus as an adverse reaction in the UK SPC. As was the case for all potential adverse reactions reported in association with Prolia, this event was subject to the company's signal detection and safety assessment processes as described above. To date, the evidence had not been sufficient to reach a conclusion about a causative relationship between mouth ulceration or oral lichen planus and Prolia to require these events to be listed in the UK SPC and PIL for Prolia. Amgen would continue to review information on Prolia.

Amgen submitted that as explained previously, the description of 'persistent pain and/or non-healing sores of the mouth or jaw' in the PIL was intended to describe in patient friendly language the rare side effect of osteonecrosis of the jaw (ONJ) which was included in the SPC. The presentation and content of the PIL for Prolia was consistent with the current law and guidance relating to PILs and had been reviewed and approved by the regulatory authority. Whilst Amgen did not believe that the description of ONJ in the PIL was inappropriate, it was currently exploring with the regulatory authority whether the existing description could be changed to further aid patient understanding.

Amgen noted that the complainant had stated that she wished to appeal the Panel's ruling of no breach of Clause 7.6, which required that when promotional material referred to published studies,

clear references was given. The complainant had not, however, provided any reasons as to why this clause was being appealed. Amgen confirmed that clear references were provided on all promotional material, including that relating to Prolia, which referred to published studies.

Amgen noted that the complainant alleged that certain aspects of Amgen's conduct were in breach of Clause 9.1. In particular:

- Amgen permitted the national patient support group to publish incorrect information concerning Prolia;

- Amgen had not paid attention to, or acted upon, patient concerns regarding Prolia which had been posted on International internet forums.

Amgen reiterated that it had not had any involvement in the supply, creation or authorship of any Prolia patient materials published by the national patient support group. Amgen was careful to ensure that it maintained high standards when it interacted with patient organisations by adhering to the requirements of the Code relating to pharmaceutical companies' interactions with patient organisations (Clause 23 of the Code that was in force at the time of the complainant's complaint, Clause 24 of the current Code) and in particular, by respecting its independence.

Amgen submitted that the national patient support group material submitted by the complainant stated that it was last revised in June 2011. It formed part of a general therapy review of available osteoporosis treatments, including Prolia. The possible side effects section of the national patient support group leaflet was not inconsistent with the SPC or PIL for Prolia which was in force at the time.

Amgen submitted that it had acted in accordance with the Code's requirements relating to interactions with patient organisations and it believed that it had upheld the high standards required under Clause 9.1.

Amgen submitted that it did not manage, control or in any way influence the internet sites/blogs referenced by the complainant as part of the appeal; the messages contained were posted freely by members of the public. Pharmaceutical companies were not required to monitor internet sites that were not under their management or responsibility for potential reports of adverse reactions. However, if a company became aware of a report of a suspected adverse reaction from any non-company sponsored site it was required to assess the report to determine whether it should be reported.

Amgen confirmed that the information contained in the blog extracts which the complainant provided as part of the appeal had all been submitted to the company's safety database in accordance with its usual process for handling cases from social media. As described above, all information about possible adverse reactions to Prolia, including this type of information, contributed to the signal detection and assessment process.

Amgen submitted that it had met its obligations with respect to the information brought to its attention and accordingly it had not failed to maintain high standards as required by the Code.

Amgen noted that the complainant contended that the alleged failures to comply with Clauses 7.2 and 7.9, in particular, were prejudicial to patient safety and warranted a breach of Clause 2 of the Code.

Amgen hoped the above information demonstrated that it took the proper investigation and assessment of potential adverse medicine reactions very seriously and had appropriate mechanisms in place to do so. The safety related information in the SPC and PIL for Prolia, which had also undergone competent authority review and approval, reflected the evidence currently available. Amgen assured the complainant that the event experienced by her as well as all other reported potential adverse reactions were considered as part of the company's ongoing monitoring of safety information and that Amgen took appropriate steps to include information on possible risks in the SPC and PIL when medically and scientifically indicated and approved by the regulatory authority.

In summary, Amgen submitted that it had complied with the Code and with its obligations under current safety legislation and good pharmacovigilance practices and that the company had addressed the complainant's appeal of the Panel's rulings of no breach of Clauses 2, 4.11, 7.2, 7.6, 7.9 and 9.1.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant alleged that Amgen had not answered questions in relation to how long a patient had been treated with Prolia before the spontaneous fractures occurred. Amgen had also failed to reply in respect of informing patients regarding the deterioration of bone density. Once this treatment had ceased, there was no mention of this fact in any of the material promoted by Amgen. Amgen had not confirmed that the relevant information for the package was made available or that there was warning of potential adverse reactions before treatment. The company confirmed that details of mouth ulceration and non-healing sores were available to patients in Canada. In its previous submissions Amgen clearly stated that it had no plans for future updates. The complainant noted that Amgen stated that in respect of the national patient support group as to not being involved in the production of any literature, yet Amgen still referred patients to the national patient support group.

The complainant alleged that Amgen's response to the appeal was at variance and did not concur with its response to the complaint.

The complainant alleged that Amgen had admitted it tailored the details of adverse reactions where it could, in order that the minimal details were released. This, of course, was couched in favour of the company's medicine.

The complainant noted that the national patient support group advised patients to exercise in a more gentle form, more suitable for the elderly, whose problems it understood as it worked with them daily.

The complainant noted that Amgen admitted that it used Prolia on a 'worldwide' basis, yet claimed to have no knowledge of the complaints she had sent to it.

Amgen admitted it was aware of the serious, life threatening consequences of continuing its use. Yet after the initiation of the complaint Amgen stated that it did not or could not find the complaints in other countries. Where patients suffered the same adverse reactions as the complainant and, in some cases even worse, but Amgen intended to use the information forwarded by the complainant. The complainant alleged that Amgen purported to be so thorough and concerned for patient welfare, it should have been aware of these complaints when initiated a considerable time ago on the various websites available to be read.

The complainant noted that Amgen stated it would continue to monitor it. It gave the complainant no reassurance that Amgen would take any constructive action to help prevent Prolia's painful path through patients worldwide.

APPEAL BOARD RULING

The Appeal Board considered that patient safety was extremely important. The Appeal Board noted that this was an emotive and important personal issue for the complainant; it was an unfortunate case and the Appeal Board expressed its sympathy for the complainant. However, the Appeal Board noted that its responsibility was to consider this case with regard to the requirements of the Code.

The Appeal Board noted that the complainant raised a number of issues which were not covered by the Code.

The Appeal Board noted Amgen's submission that the EU determined whether an adverse event should be listed in an SPC based, *inter alia*, on the likelihood of a causal relationship with use of the medicine following an analysis of all the available safety data. In that regard, the Appeal Board noted Amgen's submission that in Canada the situation was different in that all possible adverse reactions reported by patients taking the medicine in clinical trials were included in the equivalent document to the SPC, regardless of whether the reaction was related to the medicine or not. The Appeal Board recognised that it might be confusing for the complainant to see different adverse reactions reported in SPCs or equivalent for Prolia in different countries. However, the Appeal Board noted that the contents of SPCs and their equivalents in other countries such as Canada were a matter for each country's regulators.

The Appeal Board noted that the supplementary information to Clause 22.2 stated that the requirements of Clause 7 relating to information, also applied to information to the public. The Appeal Board noted that the patient leaflet dated March 2012 listed as a rare side effect 'persistent pain and/or non-healing sores of the mouth or jaw'. The Appeal Board noted from the representatives of Amgen at the appeal that this wording had been agreed with the regulators as a patient friendly description of osteonecrosis of the jaw as listed on the SPC. The Appeal Board considered that it might not be obvious that this description on the PIL did not cover mouth ulcers or sores arising from anything other than osteonecrosis of the jaw and noted that the Amgen representatives at the appeal stated that the company was discussing with the EMA a possible change to this wording to make the position clearer. The Appeal Board noted that, in any event, the content of SPCs and PILs was a matter for the regulators.

The Appeal Board noted that Amgen had written to the complainant and her treating physician and the company's submission that it had added her reported adverse event to its central files in line with regulatory requirements. The Appeal Board did not consider that the correspondence sent by Amgen to the complainant was misleading or otherwise an unfair reflection of the SPC with regard to adverse events and the complainant's experience with mouth ulceration and suspected lichen planus. The Appeal Board upheld the Panel's ruling of no breach of Clauses 7.2 and 7.9. The appeal on this point was unsuccessful.

The Appeal Board noted there were no reasons provided for the appeal regarding Clause 7.6. No promotional material had been provided by the complainant. Consequently the Appeal Board upheld the Panel's ruling of no breach of that clause. The appeal on this point was unsuccessful.

The Appeal Board again noted that it had not been provided with any promotional material, consequently it upheld the Panel's ruling of no breach of Clause 4.11 with regard to the display of the inverted black triangle symbol. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and rulings above. The Appeal Board noted the complainant's concern but considered that Amgen had not failed to maintain high standards and it upheld the Panel's ruling of no breach of Clause 9.1. The Appeal Board consequently upheld the Panel's ruling of no breach of Clause 2. The appeal on both points was unsuccessful.

Complaint received **20 October 2013**

Case completed **19 February 2014**

CASE AUTH/2646/10/13

ANONYMOUS HEALTH PROFESSIONAL v MERCK SHARP & DOHME

Sponsorship of health screening

An anonymous, non-contactable health professional referred to a public health fair (Health Mela) that he/she attended and noted that a major attraction of the event was health screening with a focus on the NHS health checks for heart diseases and diabetes. The complainant submitted that the arrangements for patient confidentiality were poor and that he/she noticed a number of Merck Sharp & Dohme representatives hovering around the patient screening area. The complainant alleged that the representatives appeared to monitor the screening and engaging with the public whilst they were waiting.

The complainant submitted that the representatives were interested because Merck Sharp & Dohme had paid for some of the screening resources. The complainant alleged that they were clearly trying to gauge the effect of the screening and the results. The complainant was concerned that the representatives were actively engaged with patient screening and learning patient details and that Merck Sharpe & Dohme's involvement with the screening had not been declared either at the event itself or on flyers.

The detailed response from Merck Sharp & Dohme is given below.

The Panel noted that the meeting poster provided by the complainant gave details of the health fair and listed activities including certain health checks and counselling. At the bottom the poster stated 'Working towards healthier living in partnership with:' which was followed by 14 organisation/ company logos. Merck Sharp & Dohme's logo did not appear. Conversely, the poster provided by Merck Sharp & Dohme included the company logo.

It was not clear where the complainant had obtained his/her poster; the Panel was unable to contact the complainant for more information. Merck Sharp & Dohme provided a summary of a telephone conversation with the event organiser who stated that there were approximately 4 versions of the poster.

The Panel noted that the accounts of the events differed between the complainant and the respondent. The Panel considered that supporting the health fair *per se* was not necessarily unacceptable; pharmaceutical company involvement had to comply with the Code.

According to the joint working agreement documentation which covered the meeting, Merck Sharp & Dohme's support included project management for each of the three events to optimize efficient cholesterol screening; help to promote the Health Mela to mosques and financial support for cholesterol screening of attendees at all three events. Merck Sharp & Dohme's financial support was limited to the hire of LDX machines and purchase of disposables for the three meetings. Merck Sharp & Dohme stated that only the machines and consumables had been paid for. No additional support was provided. This differed from the joint working agreement.

The Panel decided that the representatives had attended in a professional capacity and Merck Sharp & Dohme was responsible for their attendance. The Panel was concerned that the representatives had not worn badges to identify themselves as Merck Sharp & Dohme employees. Contrary to the complainant's view, Merck Sharp & Dohme and the organiser were clear that the two representatives had not watched the health screening. It was unclear how the organiser would be able to comment on this so definitely unless the representatives were closely shadowed at the event.

The Panel noted that there was no briefing material for the representatives regarding their attendance at the Health Mela; they had not promoted any products and according to Merck Sharp & Dohme they had not discussed work matters with those health professionals to whom they spoke. It would have been helpful if the company had provided them with clear instructions for their attendance. This was especially so as one of the representatives' managers had suggested attendance and the company's involvement in the event. In the Panel's view it should have been made abundantly clear to the representatives that they were attending in an official capacity. The layout of the rooms meant that the screening appeared to be very public and potentially people could listen in. Those being screened would be aware of the public nature of this before deciding to proceed, although they would not have known that the representatives were in the room where the screening took place. Contrary to the complainant's assertion, Merck Sharp & Dohme submitted that the representatives did not go near to, interact with or get involved with the screening.

Although the Panel has serious concerns about the representatives' attendance and conduct as outlined above, it did not consider that the complainant had established that they had actively engaged with patient screening and on this narrow ground the Panel ruled no breach of the Code. The Panel was also concerned about the failure to provide any briefing material for an event which involved the

public, which the representatives had been asked to attend and with which the company was involved but, given the wording of the Code, this did not amount to a breach and no breach was ruled.

With regard to the declaration of Merck Sharp & Dohme's involvement, the Panel noted that the flyer provided by the complainant did not have the company logo. The Panel noted its comments above in this regard. It also noted the submission from Merck Sharp & Dohme that the flyer used for the meeting included the company logo. Further there was stated to be a notice on the table and registration desk. Merck Sharp & Dohme had not been able to obtain a copy of this document.

The Panel considered that although attendees would know that Merck Sharp & Dohme had supported the event it was not sufficiently clear that those being screened would understand the extent of the company's involvement. The position was not helped as the company had been unable to provide a copy of the material made available at the registration desk. The poster provided by the complainant bore no declaration and that provided by Merck Sharp & Dohme bore a corporate logo alongside 'Working towards healthier living in partnership with:'. The Panel did not consider that the phrase and corporate logo in the poster provided by Merck Sharp & Dohme were a clear declaration of sponsorship as required by the Code; neither document complied with the Code and thus a breach was ruled.

The Panel considered that when interacting with the public at events sponsored by companies, it was extremely important to ensure that the requirements of the Code were met. Any company attendees, particularly representatives, should be given clear instructions about such involvement. The Panel noted its criticisms about the representatives and the failure to clearly disclose Merck Sharp & Dohme's involvement. It considered that overall high standards had not been maintained and a breach of the Code was ruled. The Panel did not consider that the matter brought discredit upon or reduced confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

An anonymous, non-contactable health professional complained about a public health fair (Health Mela) held in October 2013.

COMPLAINT

The complainant stated that he/she went to the public health fair out of curiosity after being told about it by a patient and finding marketing for it on the internet, a copy of which was provided. These events often raised more questions than answers for patients and so it was wise to look at what was being done.

The complainant submitted that part of the event, or in fact a major attraction of it, was health screening with a focus on the NHS health checks for heart diseases and diabetes. The complainant watched the screening with some concern as patients were easily seen and heard being tested and counselled. Patient confidentiality was a priority.

The complainant stated that he/she noticed a number of Merck Sharp & Dohme representatives hovering around the patient screening and listening intently and alleged that they appeared to be monitoring the screening process and even engaged with the public whilst they were waiting. The complainant recognised some of the people from his/her clinical practice.

From a discussion with one of the organisers, the complainant learnt that the Merck Sharpe & Dohme representative's avid interest was due to the fact that Merck Sharp & Dohme had paid for some of the resources that were being used to screen. The complainant alleged that they were clearly trying to gauge the effect of the screening and the results.

The complainant stated that this raised a number of concerns: Firstly that Merck Sharp & Dohme promotional representatives were actively engaged with patient screening and learning patient details. Secondly there was no mention at the event of the screening service being funded by Merck Sharpe & Dohme and finally there was no notice on the promotional flyer that Merck Sharp & Dohme had any involvement.

The complainant stated that that type of behaviour only served to proliferate the negative opinion of pharmaceutical companies by both professionals and public alike. The shameful behaviour of the representatives was a disgrace and the industry had not cleaned up its act.

When writing to Merck Sharp & Dohme, the Authority asked it to respond in relation to Clauses 2, 9.1, 9.10, 15.2, 15.9 and 18.4 of the Code.

RESPONSE

Merck Sharp & Dohme submitted that it carried out a full and thorough investigation including face to face interviews with the two representatives that attended as well as the lead organiser of the Health Mela. Following its investigation, Merck Sharp & Dohme was completely reassured that its representatives were nowhere near the patient screening area. In particular they did not learn or become exposed to patient information and were not monitoring, involved or interfering in any way with the health screening. Contrary to the document produced by the complainant, there was clear indication of Merck Sharp & Dohme's involvement with the meeting on the poster advertising the Health Mela, at the meeting itself and in the subsequent reports published on the organiser's website. Merck Sharp & Dohme submitted that high standards had been maintained at all times and it strongly refuted any allegations of wrong doing. There had been no breach of Clauses 2, 9.1, 9.10, 15.2 or 18.4 as alleged.

Merck Sharp & Dohme provided background to the National Forum for Health and Well Being (NFHW) and the Health Mela. The NFHW was a group that was set up by a local health users forum. In 2001, a group of health professionals and executive members of a local society set up a steering group to create an awareness of health inequalities amongst the local ethnic and social groups. The NFHW planned a community day of education, culture

and fun with an underlying objective to promote healthy living. The day was referred to as a 'Mela' – a hindu word meaning a gathering or festival. It was designed to engage the local community and mobilize and motivate members of the public to take an active and enjoyable part in their own health and well-being. The first Health Mela took place in 2001.

Since 2001 the Health Mela expanded to cover all sections of the community and became an annual event. Part of the cultural festival that was the core of the Health Mela was the work of the health olympics team. This was a group of volunteer medical students from the local university who, working under supervision, took responsibility for the Health MOT programme. It was this group that was involved in the screening on the day in question.

There were many partners in the Health Mela and the organisers stated that partnership was the trust essence of what the Health Mela was about. Partners included: Merck Sharp Dohme, another named pharmaceutical company, universities, hospitals, societies, the local council, and local TV.

A report taken from the website of the Health Mela that took place in September was provided. This was the latest report regarding a Health Mela available; the report on the Health Mela which was the subject of this complaint was not yet available.

During 2013 Merck Sharp & Dohme's involvement with the Health Mela changed. Merck Sharp & Dohme still wished to support it and provide LDX machines and consumables. The LDX machines which belonged to Merck Sharp & Dohme, that had been provided in 2012, had been disposed of. In addition, the involvement of Merck Sharp & Dohme with the Mela was now to be limited to the provision of LDX machines and consumables (ie no project management, no media support and no local marketing distribution). Merck Sharp & Dohme intended to provide LDX machines and consumables by leasing the LDX machines from a third party. Agreements were to be between the third party and the Health Mela organisers. These arrangements were documented in the minutes of the grants committee meeting, copies of which were provided. A quotation from the third party to Merck Sharp & Dohme for the provision of LDX machines and consumables was provided as was a letter of agreement between the third party and the NFHW detailing the arrangements and costs of the LDX machines and consumables.

Similar to 2012, Merck Sharp & Dohme's support of the Health Mela in 2013 was managed as a joint working project. A copy of the joint working agreement and certificate was provided.

From a head office and project perspective, it was not intended that Merck Sharp & Dohme should or would have any involvement in this activity other than to provide funding to the NFHW to supply LDX machines and associated consumables. Merck Sharp & Dohme submitted that in hindsight this project had changed from a bona fide joint working project in 2012 and would have been more appropriately classified as a grant in 2013. Despite this, Merck Sharp & Dohme submitted that the requirements of Clause 18.4 were met. The LDX machines and consumables were provided to enhance patient care and benefit the NHS. No gift, pecuniary advantage or benefit was supplied or offered to any member of the health professions or administrative staff in connection with the promotion of any medicine.

Merck Sharp & Dohme noted that blood cholesterol testing was the only health screening which it supported and it was done by the provision of funds to NFHW to hire LDX machines and consumables. It was important to recognise that that component was only a small part of the health screening provided at the Health Mela by a large number of other partners to the NFHW and the Health Mela.

After initial investigation by Merck Sharp & Dohme, it became clear that two Merck Sharp & Dohme representatives had attended the Health Mela at issue and face to face interviews were arranged to get a clear, full and accurate account of what had happened on the day and to be able to respond to the complaint. A summary of the interviews was provided.

Merck Sharp & Dohme submitted that two representatives had attended the Health Mela in October in an unofficial capacity with a view to understand more about what was involved in the Mela and to show support for the meeting organisers. There was no Merck Sharp & Dohme stand or promotion of any Merck Sharp & Dohme medicine on the day by the representatives or anyone else on behalf of Merck Sharp & Dohme. The representatives were in casual non-business dress and they had not worn name badges. Merck Sharp & Dohme further submitted that there had been no interaction between the Merck Sharp & Dohme representatives and any patients and no patient information was gleaned or obtained and/or taken away by the two representatives. The representatives did not go anywhere near, interact with or get involved with the health screening part of the Mela. No record of their attendance at the Health Mela was recorded in the Merck Sharp & Dohme customer relationship management tool by either representative.

Merck Sharp & Dohme submitted that the representatives has entered the event and registered at the desk. They then proceeded directly along past the slide room – and stands through the hall to the front of a second hall. The health screening had taken place towards the back left hand side and was screened by exhibition stands to the best of Merck Sharp & Dohme's knowledge. After the speeches and performances, the representatives went to an area in the second hall and collected a fruit smoothie. Both representatives then left the second hall, went back through the first hall, back past the slide room – and stands only to stop momentarily by the registration desk to pick up a banana before leaving the event. The representatives had attended the event for approximately one hour. A plan of the rooms, was provided.

Merck Sharp & Dohme submitted that it had had a telephone interview with a health professional, committee member of the NFHW and events organiser of the Health Mela. The summary of the conversation was provided. The events organiser confirmed that as far as he/she and his/her staff were concerned the two Merck Sharp & Dohme representatives did not go anywhere near, interact with or get involved with the health screening part of the Health Mela.

A copy of a form provided to groups and institutions by means of an invitation to potential exhibitors and participants in the Health Mela was provided as was a copy of the patient information, collection, consent and GP referral form used at the Health Mela in October. Merck Sharp & Dohme submitted that neither of the documents were Merck Sharp & Dohme materials and that its representatives have never had sight or access to those forms either blank or completed. Merck Sharp & Dohme submitted that the events organiser had ensured it that patient confidentiality was maintained at all times.

Merck Sharp & Dohme submitted that as already stated, there was no promotion of Merck Sharp & Dohme products as part of the Health Mela either by Merck Sharp & Dohme employees or on behalf of Merck Sharp & Dohme. Merck Sharp & Dohme had provided funding to hire LDX machines and consumables which were used to measure blood cholesterol. There was no link to product or promotion whatsoever with that provision. Merck Sharp & Dohme submitted that it did have a product that was licensed for the reduction of blood cholesterol, Ezetrol (ezetimibe), and a copy of the summary of product characteristics was provided.

Merck Sharp & Dohme submitted that, according to the organisers, the poster provided by the complainant was not the final version and was not the version used to advertise the Health Mela. That version had been sent to a series of stakeholders, sponsors and supporters for review and comment before the final version was produced. Merck Sharp & Dohme submitted that whilst that version of the poster did not contain the Merck Sharp & Dohme logo, the version of the poster used to advertise the Health Mela and that was available on the NFHW website did. During the telephone interview, the events organiser confirmed that attendees were informed about Merck Sharp & Dohme's involvement as the company's logo appeared on the poster and notice on the table and registration desk. Merck Sharp & Dohme had not been able to obtain a copy of the latter notice. A copy of a report from a different Health Mela produced by the NFHW with no involvement from Merck Sharp & Dohme was provided. Merck Sharp & Dohme had submitted this report as the report for the Health Mela at issue was not yet available and it provided general background and information about a very similar event. It also showed that Merck Sharp & Dohme was acknowledged on page 2 as a major partner with a further different Health Mela and Merck Sharp & Dohme logos appeared on page 6 of the report.

In combination with details on the floor plans/room layouts, Merck Sharp & Dohme provided a list of participants, exhibitors and partners involved with the 2013 Health Mela at issue.

Merck Sharp & Dohme submitted that although at the time of its response the report for the Health Mela was not yet available, there was an approximately 15 minute video of it on the nfhw website.

In conclusion Merck Sharp & Dohme submitted that even though the two representatives had not attended the Health Mela at issue in an official capacity, they had at all times maintained high standards of ethical conduct. The representatives did not attend the meeting in a promotional context and no promotion of any Merck Sharp & Dohme product had taken place. As such, no briefing materials were prepared for the representatives in relation to that activity and Merck Sharp & Dohme submitted that there had not been a breach of Clauses 15.2 or 15.9.

Merck Sharp & Dohme submitted that neither it nor its representatives had been given access to data/records that could identify or be linked to particular patients before, during or after the event. Merck Sharp & Dohme submitted that that patient confidentiality and the data protection legislation had been complied with by it and its representatives at all times. Merck Sharp & Dohme submitted that the provision of the LDX machines and associated consumables was not connected to any Merck Sharp & Dohme product or Merck Sharp & Dohme product promotion. They were provided to enhance patient care and benefit the NHS. They were not provided to an individual for personal benefit and were not an inducement to prescribe. As a result Merck Sharp & Dohme submitted that there had been no breach of Clause 18.4.

The involvement of Merck Sharp & Dohme appeared by means of a logo not only on the poster which advertised the Health Mela but also, according to the meeting organiser, at the registration desk at the meeting. Merck Sharp & Dohme submitted that its involvement with the day was displayed in a way that was proportionate to the company's involvement and in consideration of all other sponsors, participants, partners and supporters of the day. Merck Sharp & Dohme submitted that the appearance of its logo and acknowledgement of its involvement in the materials associated with the Health Mela and on the day was reasonable and as such Merck Sharp & Dohme submitted that there had been no breach of Clause 9.10.

Merck Sharp & Dohme submitted that as a result, it considered that high standards had been maintained at all times and that the reputation and confidence in the industry had not been compromised. Merck Sharp & Dohme submitted that there had been no breach of Clauses 9.1 or 2.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints,

judged on the evidence provided by the parties. Complainants had the burden of proving their complaint on the balance of probabilities. The Panel noted that as the complainant was anonymous and non-contactable it was not possible to ask him/her for further information.

The Panel examined the material provided by the complainant. This gave details of the Health Mela and that it was free to attend. A list of activities included certain health checks and counselling including blood sugar and cholesterol testing as well as blood pressure checks. The flyer also mentioned the availability of activities for children ('Wii, smoothy bike, face painting and competitions') and complementary medicine taster workshops 'Reflexology, Reiki, Head massage, yoga etc'. At the bottom the poster stated 'Working towards healthier living in partnership with:' which was followed by 14 organisation/company logos. Merck Sharp & Dohme's logo did not appear.

The version of the poster provided by Merck Sharp & Dohme included the Merck Sharp & Dohme logo and 15 others.

It was not clear precisely where the complainant had obtained his/her poster; the complainant explained that it was from the internet. The Panel was unable to contact the complainant for more information. However the Panel noted that Merck Sharp & Dohme had provided a summary of a telephone conversation with the lead organiser of the event who stated that there were approximately 4 versions of the poster. The Mela had so many partners who all wanted changes and there was limited space, time and funds to produce the poster.

The Panel noted that the accounts of the events differed between the complainant and the respondent. The Panel considered that supporting the Health Mela *per se* was not necessarily unacceptable. Any pharmaceutical company involvement had to comply with the Code.

According to the joint working agreement documentation which covered the Melas, Merck Sharp & Dohme's support included project management for each of the three events to optimize efficient cholesterol screening; assistance in promoting one Mela to mosques and financial support for cholesterol screening of attendees at all three events. Merck Sharp & Dohme's total financial support was limited to £3,556.01 for the hire of LDX machines and purchase of disposables. The actual cost of the machine and consumables for the three meetings according to the invoice was £3,345.01 plus VAT (£4,014.01). Merck Sharp & Dohme stated that only the machines and consumables had been paid for. No additional support was provided. This differed from the joint working agreement.

The Panel noted that Merck Sharp & Dohme had considered its support of the Mela in question was a joint working arrangement. The Panel did not necessarily agree that this was so. In its response to the complaint Merck Sharp & Dohme stated that this project would have been more appropriately classified as a grant in 2013. However this was not the subject of complaint so the Panel did not consider this point further. Merck Sharp & Dohme needed to be clearer about the basis of its support and to ensure the documentation was consistent with what actually happened.

The Panel noted that two Merck Sharp & Dohme representatives attended the Health Mela. Merck Sharp & Dohme provided details of their movements whilst at the Health Mela and explained that they attended in an unofficial capacity. It was not entirely clear whether the representatives were attending in a professional or personal capacity. The representatives had attended to understand what was involved and to show support for the meeting organisers. One of the representatives explained that her manager had suggested she attend. The other representative explained that she had attended primarily as a relationship development exercise. The reason for attending with the first representative was that he/she knew some of the organising committee. The Panel decided that the representatives had attended in a professional capacity and the company was responsible for their attendance. The Panel was concerned that the representatives had not worn badges to identify that they were Merck Sharp & Dohme employees. Both the company and the organiser were clear that the two Merck Sharp & Dohme representatives had not watched the health screening whereas the complainant had a different view. It was unclear how the organiser would be able to comment on this so definitely unless the representatives were closely shadowed at the event.

In cases like this it was often helpful, prior to the Panel making a ruling, to ask the complainant to comment on the company's response. This was not possible as the complainant was non-contactable. The Panel noted that there was no briefing material for the representatives regarding their attendance at the Health Mela. No products had been promoted by the representatives and according to Merck Sharp & Dohme they had not discussed work matters with those health professionals to whom they spoke. It would have been helpful if the company had provided clear instructions to the representatives attending the event. This was especially so given one of the representatives' managers had suggested attendance and the company's involvement in the event. In the Panel's view it should have been made abundantly clear to the representatives that they were attending in an official capacity. The layout of the rooms meant that the screening appeared to be very public and potentially people could listen in to the screening. Those deciding to be screened would be aware of the public nature of this before deciding to proceed, although they would not have known that the representatives were in the room where the screening took place. Contrary to the complainant's assertion, Merck Sharp & Dohme submitted that the representatives did not go near to, interact with or get involved with the screening.

The Panel has serious concerns about the representatives' attendance and conduct at the Mela as outlined above. However the Panel did not consider that the complainant had established that the representatives had actively engaged with

patient screening and on this narrow ground the Panel ruled no breach of Clause 15.2. The Panel considered that the failure to provide any briefing material at an event which involved the public, which the representatives had been asked to attend and with which the company was involved was concerning but given the wording of Clause 15.9, this did not amount to a breach of that clause. No breach was ruled.

With regard to the declaration of Merck Sharp & Dohme's involvement, the Panel noted that the flyer provided by the complainant did not have the company logo. The Panel noted its comments above in this regard. It also noted the submission from Merck Sharp & Dohme that the flyer used for the meeting included the Merck Sharp & Dohme logo. Further there was said to be a notice on the table and registration desk. Merck Sharp & Dohme had not been able to obtain a copy of this document.

The Panel noted the requirements of Clause 9.10 and considered that although attendees would be aware that Merck Sharp & Dohme had supported the event it was not sufficiently clear that those being screened would immediately understand the extent of the company's involvement. The position was not helped as the company had been unable to provide a copy of the material made available at the registration desk. The poster provided by the complainant bore no declaration and that provided by Merck Sharp & Dohme bore a corporate logo alongside 'Working towards healthier living in partnership with:'. The Panel did not consider that the phrase and corporate logo in the poster provided by Merck Sharp & Dohme were a clear declaration of sponsorship as required by Clause 9.10. Neither document complied with Clause 9.10 and thus a breach of that clause was ruled.

The Panel considered that when interacting with the public at events sponsored by companies, it was extremely important to ensure that the requirements of the Code were met. Any company attendees, particularly representatives, should be given clear instructions about such involvement. The Panel noted its criticisms about the representatives and the failure to clearly disclose Merck Sharp & Dohme's involvement. It considered that overall high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that the matter brought discredit upon or reduced confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

Complaint received **20 October 2013**

Case completed **19 February 2014**

CASE AUTH/2650/11/13

BRISTOL-MYERS SQUIBB and PFIZER v BAYER

Promotion of Xarelto

Bristol-Myers Squibb and Pfizer complained about a Xarelto (rivaroxaban) exhibition panel and promotional booklet used by Bayer at the Eurostroke Conference. Eliquis (apixaban) jointly marketed by Bristol-Myers Squibb and Pfizer and Xarelto were both anticoagulants indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

The detailed response from Bayer is given below.

The exhibition panel featured the claim at issue 'Xarelto … Highly Effective Protection From Day One' below the headline 'Efficacy matters:' and was followed by a bar chart which compared the efficacy of Xarelto with that of warfarin. Bristol-Myers Squibb and Pfizer alleged that the claim was exaggerated and could not be substantiated. Whilst Xarelto might exhibit some Factor Xa (FXa) inhibition on day one, 'protection' implied that strokes could be prevented on day one which could not be substantiated. Additionally 'highly effective' from day one was also exaggerated and could not be substantiated.

The Panel noted that the bar chart depicted the results of Patel *et al* (2011) and showed that Xarelto was non-inferior to warfarin for the primary endpoint of stroke or systemic embolism. The Panel noted Bayer's submission that the anticoagulant effect of Xarelto was due to its inhibition of FXa and that maximum inhibition (and Cmax) occurred within hours of dosing. Warfarin inhibited the synthesis of vitamin K dependent coagulation factors and although anticoagulation effects occurred within 24 hours, peak anticoagulation might be delayed 72 to 96 hours. The Panel acknowledged that inhibition of FXa would prevent clotting and thus protect patients from stroke and systemic embolism and in that regard, Xarelto exhibited maximum inhibition on day one. Nonetheless, efficacy of Xarelto was measured in terms of the prevention of stroke and systemic embolism – inhibition of FXa was not, in itself, a measure of efficacy. In the Panel's view, the claim at issue, under the heading 'Efficacy matters:' implied that on day one, Xarelto had a direct measurable effect on the prevention of stroke and systemic embolism. This was not so. The Panel considered that the claim was exaggerated and could not be substantiated and breaches of the Code were ruled.

With regard to the promotional booklet, Bristol-Myers Squibb and Pfizer submitted that, on page 4, only favourable secondary endpoints had been given prominence. It was not clear that the primary endpoint (stroke and systemic embolism) was non-inferior to warfarin. The primary safety analysis in Patel *et al*, 'major and non-major clinically relevant bleeding' and the safety endpoint, 'major bleeding', had not been included. Both of these endpoints showed no significant difference for Xarelto vs warfarin, and by omitting them clinicians were not presented with a fair and balanced overview of the safety analysis; Bristol-Myers Squibb and Pfizer alleged that Bayer had 'cherry picked' favourable data.

The complainants submitted that page 4 further stated that there were more gastrointestinal bleeds vs warfarin but there was no quantification of the increased risk or p-values to demonstrate that the increased risk was statistically significant.

Bristol-Myers Squibb and Pfizer were concerned about the claim on the same page, 'Even in your fragile patients, Xarelto has an established safety profile' and noted the restrictiveness in the Code with regard to the use of the word safe and grammatical derivations thereof. The statement regarding renally impaired patients (an example of 'fragile' patients) was inconsistent with the Xarelto summary of product characteristics (SPC) and underplayed the safety data. The elderly population was also highlighted as a potential 'fragile' patient population. However, in the elderly there was a high prevalence of renal impairment and so the above concerns highlighted for renal impairment also applied to a 'fragile' elderly population. To refer to an established safety profile in these 'fragile' patients was misleading and the safety claim could not be substantiated.

The Panel noted that the booklet, entitled 'Anticoagulation: why Xarelto matters', introduced the reader to Xarelto, its four licensed indications and that it was now widely prescribed. Page 4 was headed 'A reassuring safety profile matters' and sub-headed 'Xarelto significantly reduces the risk of fatal bleeds by 50% vs warfarin in AF [atrial fibrillation]'. The page detailed the safety data from Patel *et al* which compared Xarelto and warfarin.

The Panel noted the allegation that page 4 did not refer to the primary [efficacy] endpoint (stroke and systemic embolism) or make it clear that this endpoint was non-inferior to warfarin. The Panel noted that page 4 dealt with safety issues of the two medicines and featured a bar chart which depicted bleeding events where there was a significant advantage for Xarelto vs warfarin. In that regard the Panel did not consider that the lack of efficacy data was misleading, particularly when that data showed Xarelto to be non-inferior to warfarin. In the Panel's view, health professionals would not be misled into prescribing a product which Bayer claimed to have a 'reassuring safety profile' but which was less efficacious than the competitor to which it was compared. No breach of the Code was ruled.

The Panel noted that below the bar chart there was a claim 'Comparable safety profile vs warfarin

with an increased risk of bleeding from GI [gastrointestinal] sites'. The Panel noted that during inter-company dialogue Bayer had agreed to add the p-value to the claim in question and thus this matter was not considered by the Panel. The Panel noted however, that the increased risk of bleeding from GI sites had not been quantified in the same way as the decreased risk of other bleeding events had been in the bar chart (event rate, relative risk and p-values). In the Panel's view the failure to give readers the comparable data for GI bleeding was misleading and a breach of the Code was ruled.

In the Panel's view the claim, 'Even in your fragile patients, Xarelto has an established safety profile', did not imply that Xarelto was safe to use in fragile patients – it referred to the safety profile of the medicine and was not an absolute claim for safety. The Panel ruled no breach of the Code. The Panel considered that the claim could be substantiated and no breach of the Code was ruled. Given these two rulings, the Panel did not consider that Bayer had failed to maintain high standards and ruled accordingly.

The Panel noted that following the claim about fragile patients, those with moderate to severe renal impairment and the elderly (≥75 years) were listed as examples of such patients. The Panel noted that Xarelto could be prescribed to those with a creatinine clearance as low as 15ml/min (severe renal impairment) or more but was not recommended for patients with a creatinine clearance of <15ml/min (renal failure). The Panel further noted the reference to elderly patients as a separate group and that many of them would have some degree of renal impairment. Age alone, however, was not a reason to reduce the dose of Xarelto. As above, the Panel did not consider that the reference to an established safety profile in the elderly or those with moderate or severe renal impairment was a claim for absolute safety in either group. No breach of the Code was ruled. The Panel considered that the claim could be substantiated; no breach of the Code was ruled. The Panel did not consider that Bayer had failed to maintain high standards and ruled no breach of the Code.

Bristol-Myers Squibb and Pfizer alleged that page 5 underplayed the complexity of anticoagulation treatment for patients and clinicians, whereby stroke prevention had to be balanced against the risk of bleeding; the heading 'Simplicity matters' was an all-embracing, general claim and implied that using Xarelto was simple. Page 5 also included the claim 'Once-daily Xarelto provides fast-acting, 24 hour protection'. As described above, Bristol-Myers Squibb and Pfizer did not consider that it could be adequately substantiated and was an exaggerated claim.

The Panel noted that page 5 was headed 'Simplicity matters' and sub-headed in emboldened text, 'A once-daily novel oral anticoagulant that provides 24hr protection …'. The sub-heading continued further down the page with '… without the need to adjust dose for a patient's age, gender or body weight' which was similarly emboldened. There then followed a description of the dosage regimen; one 20mg tablet once-daily (with food) for patients with atrial fibrillation and one 15mg table once-daily (with food) for atrial fibrillation patients with moderate or severe renal impairment. The Panel noted that the heading 'Simplicity matters' was on a page which clearly dealt with the once-daily dosing regimen of Xarelto. The Panel considered that the intended audience (nurses, payors, pharmacists and physicians) would be well acquainted with the complexities of warfarin therapy; the dosing regimen and monitoring of Xarelto patients was not as complicated. In the Panel's view, health professionals would know that with any anticoagulant, the risk of unintended bleeding had to be balanced against stroke prevention. The Panel did not consider that 'Simplicity matters' underplayed the complexity of anticoagulant therapy as alleged. No breach of the Code was ruled. The Panel did not consider that Bayer had failed to maintain high standards and no breach of the Code was ruled .

With regard to the claim 'Once-daily Xarelto provides fast-acting, 24 hour protection', the Panel noted its comments above. The Panel considered that, contrary to Bayer's submission, the claim implied that Xarelto had been shown to have a fast and measurable effect on the prevention of stroke and systemic embolism. In the Panel's view this was not so. The Panel thus considered that the claim was exaggerated and could not be substantiated and breaches of the Code were ruled.

Bristol-Myers Squibb and Pfizer noted that the sub-heading to page 6 was, 'Once-daily dosing improves compliance …'. Bristol-Myers Squibb and Pfizer submitted that the page was misleading and could imply that once-daily novel oral anticoagulants (NOACs) (such as Xarelto) offered improved compliance vs twice-daily NOACs (such as Eliquis).

A disclaimer stated 'Not based on Xarelto data'. This page was referenced to Coleman *et al* (2012) which evaluated adherence rates of chronic cardiovascular therapy based on three criteria (taking adherence, regimen adherence, timing adherence). However, Bayer used the timing adherence results only, where the difference between once-daily and twice-daily dosing was the largest. The other two adherence results were not included on the page, and therefore this data had been generalised implying that these results referred to overall treatment adherence. Furthermore, Coleman *et al* indicated several limitations to their analysis. Bristol-Myers Squibb and Pfizer considered that the claim could [sic] be substantiated and therefore should not be used.

The Panel noted that page 6 was headed 'Compliance matters' and sub-headed 'Once-daily dosing improves compliance …'. This was followed by a chart which showed that 76.3% of patients complied with once-daily dosing vs 50.4% with twice-daily dosing. A highlighted box to the right-hand side of the chart featured the claim '25% increase in treatment adherence in once-daily vs twice-daily regimens'. The chart and claim were

based on the results of Coleman *et al*, a pooled analysis of 29 studies of patients taking chronic cardiovascular therapy including anticoagulants. The x axis of the chart was labelled 'Dosing frequency – Not based on Xarelto data'. In the Panel's view, given the context in which it appeared, the chart implied that it had been unequivocally shown that 76.3% of patients would comply with once-daily Xarelto therapy vs 50.4% of patients taking a twice-daily alternative. This was not so; the Panel considered that such an implication was misleading and could not be substantiated. A breach of the Code was ruled. The Panel considered that high standards had not been maintained and a breach of the Code was ruled.

Bristol-Myers Squibb and Pfizer noted the claim on page 8, 'Xarelto provides simple, proven, predictable anticoagulation for stroke prevention in non-valvular AF'. As stated above, 'simple' in that context inferred an all-embracing general claim and suggested that Xarelto was simple to use. Bristol-Myers Squibb and Pfizer submitted that this underplayed the complexity of anticoagulation treatment. Furthermore, the page demonstrated further 'cherry picking' of positive (superior vs warfarin) secondary endpoints with omission of important and relevant safety endpoints as previously mentioned. It mentioned protection against stroke and systemic embolism but did not state this was non-inferior to warfarin which was the primary endpoint of the study or that major bleeding was non-inferior to warfarin.

The Panel noted that page 8 was headed 'When it really matters' followed by the sub-heading 'Xarelto provides simple, proven, predictable anticoagulation for stroke prevention in non-valvular AF'. The first bullet point 'Simplicity matters' referred to the once-daily dosage with no adjustment needed for age, gender or body weight. The Panel considered its comments above applied here. The Panel did not consider that 'simple' was an all-embracing claim as alleged; it was clearly linked to the Xarelto dosage regimen details of which appeared immediately beneath. No breach of the Code was ruled. The Panel did not consider that Bayer had failed to maintain high standards and ruled accordingly.

The Panel noted the general allegation of 'cherry picking' of positive data for Xarelto vs warfarin and the omission of important and relevant safety endpoints. The Panel considered that the presentation of positive data without reference to endpoints where Xarelto was 'non-inferior' to warfarin was not necessarily unacceptable. In the Panel's view page 8 did not imply that Xarelto was more efficacious than warfarin; it highlighted some areas where Xarelto had a better safety profile vs warfarin and it referred to the dosage regimen of Xarelto. The Panel, however, noted its comments above about the increased risk of bleeding from GI sites with Xarelto vs warfarin. The bullet point on page 8 entitled 'Safety profile matters' referred to the decreased risk of fatal bleeds and of devastating inter-cranial haemorrhage with Xarelto vs warfarin but not to the increased risk of bleeding from GI sites. In the Panel's view, although Patel *et al* had shown that overall Xarelto had a comparable safety profile compared with warfarin, it was important for health professionals to know that patients treated with Xarelto were at increased risk of GI bleeds vs patients on warfarin; the health professionals could thus manage that risk appropriately. The Panel considered that page 8 was misleading in that regard and a breach of the Code was ruled. The Panel considered that Bayer had failed to maintain high standards and ruled a breach of the Code.

Bristol-Myers Squibb and Pfizer complained about an Xarelto (rivaroxaban) exhibition panel (ref L.GB.02.2013.1694c, April 2013) and promotional booklet (ref L.GB.02.2013.1576c, February 2013) used by Bayer at the Eurostroke Conference in London in May. Bristol-Myers Squibb and Pfizer stated that use of certain claims should cease in all Xarelto materials exhibited at meetings, in all Xarelto advertising, and in any Xarelto promotional materials currently being used by Bayer.

Eliquis (apixaban) jointly marketed by Bristol-Myers Squibb and Pfizer and Xarelto were both anticoagulants indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Bayer explained that atrial fibrillation (AF) was the most common condition which caused irregular heartbeat. The collecting chamber of the heart ie the atrium beat irregularly and caused blood to stagnate in the atrial appendage, as a consequence of this the blood clotted in the atrial appendage. When all or part of this clot broke away, it could lodge in any blood vessel and block blood supply resulting in death of the affected tissue. The brain was the main organ affected, 15 to 20% of the strokes were associated with AF. Stroke was a devastating event particularly if it was associated with AF. Strokes associated with AF were bigger in size and patients had a 50% likelihood of death within one year.

Adequate anticoagulation could reduce the relative risk of having a stroke by 62%. Guidelines from the National Institute of Health and Care Excellence (NICE) and the European Society of Cardiology (ESC) recommended that patients with high risk of stroke should be anticoagulated. Warfarin had been the gold standard up until now but had always been perceived as difficult to manage due to the requirement of regular monitoring, drug and food interactions. There had always been a desire to have options which were at least as efficacious as warfarin but at the same time simple and convenient to use both by physician and patients. The recent development and approval of three novel oral anticoagulants, (NOACs) had increased treatment options. Other conditions which commonly required anticoagulation were deep vein thrombosis (DVT) and pulmonary embolism (PE). Heparin in combination with warfarin was used to prevent and treat these conditions. Xarelto was the only NOAC which could be used to prevent and treat DVT and PE.

A Xarelto exhibition panel (ref L.GB.02.2013.1694c, April 2013)

1 Claim 'Xarelto … Highly Effective Protection From Day One'

Below the claim was a bar chart depicting the results of Patel *et al* (2011) which showed that Xarelto was non-inferior compared with warfarin in the prevention of stroke and systemic embolism.

COMPLAINT

Bristol-Myers Squibb and Pfizer alleged that the claim was exaggerated and could not be substantiated. Whilst Xarelto might exhibit some Factor Xa (FXa) inhibition on day one (based on 2-3 half lives to reach steady state), 'protection' implied that strokes could be prevented on day one which could not be substantiated. Additionally 'highly effective' from day one was also exaggerated and could not be substantiated.

Bristol-Myers Squibb and Pfizer alleged breaches of Clauses 7.4 and 7.10.

RESPONSE

Bayer submitted that the validity of the claim 'Highly Effective Protection From Day One' rested on the interpretation of 'highly effective protection' and whether that was deliverable from the first day of treatment.

Pfizer and Bristol-Myers Squibb had complained on the basis that 'protection' implied that strokes could be prevented on day one which could not be substantiated' and that 'highly effective' was an exaggerated claim that could not be substantiated

Bayer submitted that the claim was in line with the Xarelto summary of product characteristics (SPC), opinion from the Committee for Medicinal Products for Human Use (CHMP), published literature and was supported by the mechanism of action, pharmacokinetics and pharmacodynamics of Xarelto. In addition, Xarelto had been shown to be non-inferior to warfarin, the gold standard AF treatment.

Bayer noted that as the target audience at the Eurostroke conference were specialists in stroke, it was reasonable to assume that they had a good understanding of the available treatments and were unlikely to be easily misled. Bayer submitted that 'protection' did not imply that all strokes would be prevented on day one; no product was 100% effective and certainly not on the first day of dosing. For this target audience, 'protection' could reasonably be understood to mean that the product worked from day one to reduce the risk of stroke in line with its licensed indication. Further, Xarelto was highly effective and this was supported with a strong evidence base.

In support of the above, Bayer submitted that the Atrial Fibrillation Association (AFA) booklet published in 2008 (reviewed 2012) and endorsed by the Department of Health (DoH), stated that new oral anticoagulants were effective almost immediately after taking, and large clinical trials had shown them to be as effective as warfarin in reducing the risk of stroke.

Sections 5.1 and 5.2 of the Xarelto SPC stated, 'Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi'. Protection against atrial fibrillation was achieved by inhibiting Factor Xa, in atrial fibrillation sluggish flow in the left atrium predisposed to clot formation in the atrial appendage which could embolise to brain vessels and cause stroke. Successful prevention of stroke was achieved by reducing the creation of thrombi.

Kubitza *et al* (2005a) stated 'Maximum inhibition of FXa activity was achieved 1 to 4 hours after administration of [Xarelto].'

The Xarelto SPC further stated 'In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for prothrombin time (Neoplastin) 1-4 hours after tablet intake (ie at the time of maximum effect) in patients treated with 20mg once-daily ranged from 14 to 40s'.

Kubitza *et al* (2005b) showed that in healthy caucasian males 'Maximum inhibition of FXa activity occurred approximately 3h after [Xarelto] dosing. Following the first dose of [Xarelto], maximum inhibition of FXa activity was 22% after 5mg, 33% after 10mg, 56% after 20mg, and 68% after 30mg, and inhibition was maintained for 8–12h after 5mg and for approximately 12h after the 10mg, 20mg, and 30mg doses. There were no major differences in maximum inhibition of FXa activity between the first and second daily doses, or on day 7 compared with day 0, although trough levels were increased with the 20mg and 30mg bid doses'. 'The onset of inhibition of FXa activity with [Xarelto] was rapid, with maximum effect occurring within 2–3 hours of dosing in all dosing groups'.

Graff *et al* (2007) in a placebo-controlled, randomised, crossover study in 12 healthy subjects showed maximal effect of Xarelto 2 hours after administration: prothrombinase-induced clotting time was prolonged 1.8 and 2.3 times baseline after Xarelto 5mg and 30mg, respectively. Collagen-induced endogenous thrombin potential was reduced by ~80% and ~90% compared with baseline after Xarelto 5mg and 30mg, respectively, and tissue factor-induced endogenous thrombin potential was reduced by ~40% (5mg) and ~65% (30mg), respectively. Thrombin generation remained inhibited for 24 hours'.

In contrast, the mechanism of action for warfarin was different and slow to make the desired effect. Warfarin inhibited synthesis of vitamin K dependent coagulation factors and the warfarin SPC stated, 'An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours'. There was no such lag time for Xarelto

and maximum concentration (C_{max}) appeared 2-4 hours after oral intake. Warfarin inhibited natural anticoagulants like protein C and S in addition to sequential depression of vitamin K dependent anticoagulation factors (Factors VII, IX, X and II) activities, hence the need for bridging with heparin. There was no such requirement for Xarelto, which was a specific direct FXa inhibitor and was acknowledged by the CHMP committee.

The European Medicines Agency (EMA) in its assessment report for Xarelto (22 September 2011 ref EMA/CHMP/301607/2011), under the section 'Final dose regimen chosen' stated that 'It was therefore determined that including b.i.d. dosing initially in the Xarelto regimen for the phase III program could provide the intensification needed and permit continuous Xarelto therapy without first requiring the use of a heparin in the initial acute DVT treatment phase'. Section 2.5.3, 'Discussion on clinical efficacy', stated 'It is, however, agreed with the Applicant that there is little evidence that supports a general recommendation for the use of parenteral anticoagulants in the initial phase of acute treatment. The similar time of onset after administration of the two anticoagulants is of vital importance for this conclusion'. The assessment report dated 22 September 2011 (ref EMA/42547/2012) agreed the same assumption for stroke prevention in atrial fibrillation for dose finding; 'These simulations showed that the simulated plasma Xarelto concentration-time profile for patients in the [stroke prevention in atrial fibrillation] patient population with normal renal function receiving 20mg once-daily was similar to that for patients in the DVT-T population receiving the same dose'.

This demonstrated that the CHMP did not consider the requirement of heparin for Xarelto to bridge the initial period and considered it effective from day one.

Patel *et al* and other similar trials for NOACs were event driven, non-inferiority trials. It was expected in event driven trial design that patients would have events to compare therapies in a randomised control trial. These trials were not powered to show results on a daily basis and meaningful results were obtained on the pre-specified number of events. In such trials, the primary endpoint achieved statistical significance. The Xarelto SPC stated, 'Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism'.

The fact that warfarin was highly effective in preventing stroke in patients with atrial fibrillation was well recognised in published literature including pivotal studies like Patel *et al*, Granger *et al* (2011), and many others like Shameem and Ansell (2013); Albertsen *et al* (2013); Halperin and Goyette (2012); Clase *et al* (2012); Quinn *et al* (2012); Jorgensen *et al* (2012); Mangiafico and Mangiafico (2012); Martin and Stewart (2012); Chan *et al* (2011), to cite a few from recent years.

Patel *et al* clearly showed that rivaroxaban was non-inferior to warfarin in the intention to treat (ITT) population and superior to warfarin in the per-protocol (PP) population, making it highly effective.

In summary, Xarelto was demonstrably non-inferior to the gold standard (warfarin) in its effectiveness (protection against stroke) and the mode of action delivered that protection (coagulation inhibition) within hours of the first dose. Bayer thus submitted that these claims were not exaggerated and could be substantiated and were not in breach of Clauses 7.4 and 7.10.

PANEL RULING

The Panel noted that the claim at issue appeared below the headline 'Efficacy matters:' and was followed by a bar chart which compared the efficacy of Xarelto with that of warfarin. The bar chart depicted the results of Patel *et al* and showed that Xarelto was non-inferior to warfarin for the primary endpoint of stroke or systemic embolism. Study participants were followed for a median of 707 days. In the per-protocol population, stroke or systemic embolism occurred in 188 patients in the Xarelto group (1.7% per year) and in 241 patients in the warfarin group (2.2% per year) ($p<0.001$ for non-inferiority).

The Panel noted Bayer's submission that the anticoagulant effect of Xarelto was due to its inhibition of FXa and that maximum inhibition (and C_{max}) occurred within hours of dosing. Warfarin exerted its anticoagulant effect by inhibiting the synthesis of vitamin K dependent coagulation factors. Although anticoagulation effects occurred within 24 hours of warfarin administration, peak anticoagulation might be delayed 72 to 96 hours. The Panel acknowledged that inhibition of FXa would prevent clotting and thus protect patients from stroke and systemic embolism and in that regard, Xarelto exhibited maximum inhibition on day one. Nonetheless, efficacy of Xarelto was measured in terms of the prevention of stroke and systemic embolism – inhibition of FXa was a pharmacological effect and not, in itself, a measure of efficacy. In the Panel's view, the claim at issue, under the heading 'Efficacy matters:' implied that on day one, Xarelto had been shown to have a direct measurable effect on the prevention of stroke and systemic embolism. This was not so. The Panel considered that the claim could not be substantiated. A breach of Clause 7.4 was ruled. The Panel further considered that the claim was exaggerated. A breach of Clause 7.10 was ruled.

B Xarelto promotional booklet (L.GB.02.2013.1576c, February 2013)

1 'A reassuring safety profile matters'

This statement appeared as the heading to page 4 above a bar chart which detailed safety data from Patel *et al*.

COMPLAINT

Bristol-Myers Squibb and Pfizer submitted that only favourable secondary endpoints had been given prominence on page 4 of the booklet. It was not clear that the primary endpoint (stroke and systemic embolism) was non-inferior to warfarin. The primary safety analysis in Patel *et al*, 'major and non-major

clinically relevant bleeding' and the safety endpoint, 'major bleeding', had not been included. Both of these endpoints showed no significant difference for Xarelto vs warfarin, and by omitting them clinicians were not presented with a fair and balanced overview of the safety analysis; Bristol-Myers Squibb and Pfizer alleged that Bayer had 'cherry picked' favourable data. In an inter-company letter Pfizer alleged a breach of Clauses 7.2 and 9.1.

Page 4 further stated that there were more gastrointestinal bleeds vs warfarin but there was no quantification of the increased risk or p-values to demonstrate that the increased risk was statistically significant, which it was. During inter-company correspondence Bayer agreed to add a p-value for the gastrointestinal bleeding data in future materials. However, Bayer had not agreed to present the event rates or hazard ratio in materials. Bristol-Myers Squibb and Pfizer submitted that the presentation of event rates or hazard ratios was important so that clinicians could correctly interpret that important safety endpoint. In an inter-company letter Pfizer alleged a breach of Clause 7.2.

During inter-company correspondence, Bayer agreed not to use the title of this page 'A reassuring safety profile matters'. However, Bristol-Myers Squibb and Pfizer were concerned about the claim further down the page 'Even in your fragile patients, Xarelto has an established safety profile'. The supplementary information to Clause 7.9 stated that 'The restrictions on the word "safe" apply equally to grammatical derivatives of the word such as "safety". For example, "demonstrated safety" or "proven safety"are prohibited under this clause'. In an inter-company letter Pfizer alleged a breach of Clause 7.9.

Bristol-Myers Squibb and Pfizer were concerned about the reference to 'Even in your fragile patients'. The statement regarding renally impaired patients (an example of 'fragile' patients) was inconsistent with the Xarelto SPC and underplayed the safety data. The SPC stated that in moderate renal impairment the dose of Xarelto had to be reduced to 15mg once-daily. In severe renal impairment it had to be used with caution. Xarelto was not recommended if creatinine clearance was <15ml/min. Because of increased risk of bleeding, careful monitoring for signs/symptoms of bleeding complications and anaemia was required after treatment initiation in patients with severe renal impairment (creatinine clearance 15-29 ml/min) or with moderate renal impairment (creatinine clearance 30-49 ml/min) concomitantly receiving other medicinal products which increased rivaroxaban plasma concentrations.

The elderly population was also highlighted as a potential 'fragile' patient population. However, in the elderly there was a high prevalence of renal impairment and so the above concerns highlighted for renal impairment also applied to a 'fragile' elderly population. To refer to an established safety profile in these 'fragile' patients was misleading and the safety claim could not be substantiated. In an inter-company letter Pfizer alleged a breach of Clauses 7.9 and 9.1.

In their complaint to the Authority, Bristol Myers Squibb and Pfizer summarised their concerns about the booklet as a whole and referred to: Clause 7.2 (misleading by 'cherry picking' favourable data); Clause 7.4 (claims not capable of substantiation); Clause 7.9 (safety claims not capable of substantiation and safety underplayed); Clause 7.10 (exaggerated and all-embracing claims) and Clause 9.1 (high standards not maintained).

REPSONSE

Bayer noted that Pfizer and Bristol-Myers Squibb had outlined a number of comments in relation to this page. However, Bayer failed to identify a single allegation in relation to a specific clause number. Clause 7.9 was mentioned but there was no allegation, as such. Pfizer and Bristol-Myers Squibb implied that statements such as 'proven safety' or 'demonstrated safety' were not acceptable, however Bayer had not used either of these statements in its claim. Bayer's claim was: 'Even in your fragile patients, Xarelto has an established safety profile'. This clearly referred to the overall data set available for patients in those sensitive groups, rather than a claim for the product *per se*.

Bayer noted Pfizer and Bristol-Myers Squibb's concern that the data had been 'cherry picked' because the primary endpoint (non-inferiority) was not made clear, however, there was no specific complaint on that point. Even if there were, the claims on page 4 were about safety. Since Patel *et al* showed non-inferiority, the products were comparable in terms of efficacy and therefore presenting the differences in respect of safety was not misleading (had the study failed to show non-inferiority, that might have been a different matter).

Bayer noted that Pfizer and Bristol-Myers Squibb had further commented that the presentation of p-values, hazard ratios and event rates was helpful to the reader; Bayer did not disagree, however there was no Code requirement *per se* to present those statistical reference points. Bayer submitted that it had provided all the safety information which a clinician needed to make an informed decision. Bayer agreed to include the p-value for gastrointestinal bleeding during inter-company dialogue as it was statistically significant but it was not a requirement of the Code to include p-values and event rates for each result.

Bayer noted that Pfizer and Bristol-Myers Squibb did not identify a specific clause number, but had commented generally about the phrase: 'Even in your fragile patients, Xarelto has an established safety profile'.

Bayer stated that Xarelto had an established safety profile in fragile patients. There was no claim that the product was 'safe' in this group, and no inference that it should be prescribed at the standard dose; only that the track record in this population was positive. In fact it was specifically noted in the SPC that in AF patients with moderate renal impairment and severe renal impairment, a reduction in dose was appropriate. As stated, many elderly patients

had a degree of renal impairment; however the elderly (*per se*) was not identified as a risk group for Xarelto; the SPC clearly identified patients in whom caution was appropriate because they were renally impaired, regardless of age.

The safety information in the booklet was based on 187 clinical trials in more than 90,000 patients (Bayer IMPACT database) and worldwide clinical use by over 5 million patients.

The EMA in its assessment report for Xarelto (22 September 2011 ref EMA/CHMP/ 301607/2011), considered the evidence (in the 'Special populations' section) and agreed, 'The increased exposure in the elderly was to a large extent caused by reduced renal function. Consequently dose reduction based on age alone was not considered needed. The [stroke prevention in atrial fibrillation] population consisted mostly of elderly patients and there was extensive experience in treating elderly patients with Xarelto 20mg q.d'.

Contrary to other NOACs, the Xarelto SPC placed no dose restriction for use in elderly patients.

The Eliquis SPC referred to use in the elderly and stated 'No dose adjustment required, unless criteria for dose reduction are met'. With regard to dose reduction the SPC stated 'The recommended dose of Eliquis is 2.5mg [instead of 5mg] taken orally twice-daily in patients with [non-valvular atrial fibrillation] and at least two of the following characteristics: age ≥ 80 years, body weight ≤60kg, or serum creatinine ≥1.5mg/dl (133micromole/l)'.

The Pradaxa SPC stated that the recommended daily dose was 220mg (instead of 300mg) taken as one 110mg capsule twice-daily in patients aged 80 years or above. For patients aged between 75 and 80, the daily dose of Pradaxa of 300mg or 220mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding.

Halperin *et al* (unknown date) presented the sub-analysis of Patel *et al* and concluded, 'In elderly, high-risk patients with AF, once-daily oral rivaroxaban without coagulation monitoring or dose adjustment performed favourably compared to adjusted-dose warfarin as it did in the overall [study] population'. Halperin stated no need for Xarelto dose adjustment.

With regard to renal patients Xarelto had an established safety profile as in Patel *et al* the pivotal phase III trial for Xarelto, a cohort of patients with impaired renal failure were studied with lower dose of 15mg instead of 20mg. The lower dose of Xarelto (15mg once a day) was evidence based (a large phase III clinical trial), in line with the Xarelto SPC and did not underplay the safety data.

The Xarelto SPC stated 'In patients with moderate (creatinine clearance 30-49ml/min) or severe (creatinine clearance15-29ml/min) renal impairment the following dosage recommendations apply: For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15mg once-daily (see section 5.2)'.

Fox *et al* (2011) published the sub-analysis of Patel *et al* renal impairment patients and stated 'Dose adjustment in [Patel *et al*] yielded results consistent with the overall trial in comparison with dose-adjusted warfarin'. Fox *et al* further quoted in the safety section that, 'there was no excess bleeding on rivaroxaban compared with warfarin. There was no excess in the principal safety endpoint (HR 0.98; 95% CI 0.84–1.14) or in the individual bleeding outcomes in those treated with rivaroxaban 15mg/day compared with dose-adjusted warfarin. Furthermore, in those with moderate renal insufficiency, critical organ bleeding (HR 0.55; 95% CI 0.30–1.00) and fatal bleeding (HR 0.39; 95% CI 0.15–0.99) were less frequent with rivaroxaban. The lower rate of fatal bleeding was consistent with the findings in those with preserved renal function (HR 0.55; 95% CI 0.32–0.93)'. Fox *et al* further stated that 'In patients with moderate renal insufficiency, rivaroxaban-treated patients had more frequent gastrointestinal bleeding (4.1 vs. 2.6%; p = 0.02)'.

The safety profile of Xarelto for elderly patients and patients with renal impairment was in line with the SPC and established with good clinical evidence.

PANEL RULING

The Panel noted Bayer's assertion that the complainants had not alleged breaches of any specific clauses of the Code. The Panel further noted, however, that inter-company dialogue clearly referred to relevant clauses of the Code and so the Panel used this as the basis for its ruling. In addition, specific clauses of the Code were listed in the summary of the complaint.

The Panel noted that the booklet at issue was entitled 'Anticoagulation: why Xarelto matters'. Pages 2 and 3 introduced the reader to Xarelto, its four licensed indications and that it was now widely prescribed. Page 4 was headed 'A reassuring safety profile matters' and sub-headed 'Xarelto significantly reduces the risk of fatal bleeds by 50% vs warfarin in AF [atrial fibrillation]'. The page detailed the safety data from Patel *et al* which compared Xarelto and warfarin. The principle safety endpoint in Patel *et al* was a composite of major and non-major clinically relevant bleeding events; such events occurred in 14.9% of Xarelto patients vs 14.5% of warfarin-treated patients (p=0.44). Rates of major bleeding were similar in the two groups (3.6% and 3.4% respectively, p=0.58) although major bleeding from gastrointestinal sites occurred more frequently in the Xarelto group (3.2% vs 2.2%, p<0.001).

The Panel noted the allegation that the page at issue did not refer to the primary [efficacy] endpoint (stroke and systemic embolism) or make it clear that this endpoint was non-inferior to warfarin. The Panel noted that the page at issue dealt with safety issues of the two medicines and featured a bar chart which depicted bleeding events where there was a

significant advantage for Xarelto vs warfarin. In that regard the Panel did not consider that the lack of efficacy data was misleading, particularly when that data showed Xarelto to be non-inferior to warfarin. In the Panel's view, health professionals would not be misled into prescribing a product which Bayer claimed to have a 'reassuring safety profile' but which was less efficacious than the competitor to which it was compared. No breach of Clause 7.2 and 9.1 was ruled.

The Panel noted that below the bar chart there was a claim 'Comparable safety profile vs warfarin with an increased risk of bleeding from GI [gastrointestinal] sites'. The Panel noted that during inter-company dialogue Bayer had agreed to add the p-value to the claim in question and thus this matter was not considered by the Panel. The Panel noted however, that the increased risk of bleeding from GI sites had not been quantified in the same way as the decreased risk of other bleeding events had been in the bar chart (event rate, relative risk and p-values). In the Panel's view the failure to give readers the comparable data for GI bleeding was misleading and a breach of Clause 7.2 was ruled.

The Panel noted the claim 'Even in your fragile patients, Xarelto has an established safety profile'. In the Panel's view the claim did not imply that Xarelto was safe to use in fragile patients – it referred to the safety profile of the medicine and was not an absolute claim for safety. The Panel ruled no breach of Clause 7.9. The Panel considered that the claim could be substantiated and no breach of Clause 7.4 was ruled. Given these two rulings, the Panel also ruled no breach of Clause 9.1.

The Panel noted that following the claim about fragile patients, those with moderate to severe renal impairment and the elderly (≥75 years) were listed as examples of such patients. With regard to renal impairment, the Panel noted that Xarelto could be prescribed to those with a creatinine clearance of 15ml/min (severe renal impairment) or more. The medicine was not recommended for patients with a creatinine clearance of <15ml/min (renal failure). The Panel further noted the reference to elderly patients as a separate group and that many of them would have some degree of renal impairment. Age alone, however, was not a reason to reduce the dose of Xarelto. As above, the Panel did not consider that the reference to an established safety profile in the elderly or those with moderate or severe renal impairment was a claim for absolute safety in either group. No breach of Clause 7.9 was ruled. The Panel considered that the claim could be substantiated; no breach of Clause 7.4 was ruled. The Panel also ruled no breach of Clause 9.1.

2 'Simplicity matters'

This statement appeared as the heading to page 5.

COMPLAINT

Bristol-Myers Squibb and Pfizer alleged that page 5 underplayed the complexity of anticoagulation treatment for patients and clinicians, whereby stroke prevention had to be balanced against the risk of bleeding. During inter-company correspondence Bayer referred to Case AUTH/2537/10/12 - Anonymous v Bayer, where Bayer was not found in breach for the claim 'one tablet, once-daily, simple'. However, the page title was a very different claim to the one in the case report. Bristol-Myers Squibb and Pfizer alleged that the heading 'Simplicity matters' was an all-embracing, general claim. Bristol-Myers Squibb and Pfizer considered that the implication was that using Xarelto to manage a patient's anticoagulation was a simple matter. Furthermore, in the Xarelto SPC it stated 'Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period'. Bristol-Myers Squibb and Pfizer were concerned that the page could imply that once Xarelto was prescribed, few other considerations were needed as it was so simple. In an inter-company letter Pfizer alleged a breach of Clauses 7.9 and 9.1.

Page 5 also included the claim 'Once-daily Xarelto provides fast-acting, 24 hour protection'. As described above, Bristol-Myers Squibb and Pfizer did not consider that it could be adequately substantiated and was an exaggerated claim. Pharmacodynamic studies of FXa inhibition could not be extrapolated to imply 'fast acting' stroke prevention. In an inter-company letter Pfizer alleged a breach of Clauses 7.4 and 7.10.

In their complaint to the Authority, Bristol Myers Squibb and Pfizer summarised their concerns about the booklet as a whole and referred to: Clause 7.2 (misleading by 'cherry picking' favourable data); Clause 7.4 (claims not capable of substantiation); Clause 7.9 (safety claims not capable of substantiation and safety underplayed); Clause 7.10 (exaggerated and all-embracing claims) and Clause 9.1 (high standards not maintained).

RESPONSE

Bayer noted that Pfizer and Bristol-Myers Squibb had not identified any clauses of the Code in relation to the above and so Bayer's comments were of a general nature in the absence of any specific allegation.

Some general points had been made by Pfizer and Bristol-Myers Squibb, however their comments were not correct and out of context.

The page had two bold headings under the main heading of 'Simplicity matters'; 'A once-daily novel oral anticoagulant that provides 24hr protection…' and '…without the need to adjust dose for a patient's age, gender or body weight'.

Bayer noted that Pfizer and Bristol-Myers Squibb discussed the claim: 'Once-daily Xarelto provides fast-acting, 24-hour protection'. As already indicated, Xarelto had an inhibitory effect within hours of the first dose, had demonstrated 24-hour duration of action and in inhibiting FXa, worked to reduce the risk of stroke in line with the licensed indication; the claim did not imply that strokes were prevented quickly. The argument for 'fast acting'

had been discussed earlier. '24-hour protection' was based on the results of clinical trials, and a brief account was given below.
In Patel *et al*, a once-daily dose was used to provide protection to patients and was shown to be non-inferior to warfarin. Warfarin reduced the relative risk of stroke in patients with atrial fibrillation by 62%. The evidence that Xarelto was superior to warfarin in per-protocol analysis and non-inferior to warfarin in ITT analysis, demonstrated that once-daily Xarelto provided protection for 24 hours. No other NOAC had shown benefit of once a day dose in a clinical trial.

The EMA in its assessment report for Xarelto (22 September 2011 ref EMA/CHMP/301607/2011), stated 'Another study identified a prolonged influence of rivaroxaban beyond 24h on the peak level of the [endogenous thrombin potential] as well as lag time suggesting that pharmacological effects may be present beyond 24 hours after doses of 20mg'.

Graff *et al* stated 'Thrombin generation remained inhibited for 24 hours'.

Both claims on page 5 were in line with the Xarelto SPC, which stated, that in the indication of stroke prevention in patients with non-valvular atrial fibrillation, the randomised controlled trial was designed to show efficacy at once a day dose. The results demonstrated that once a day dose was non-inferior to warfarin. It also stated that no dose adjustment was required for patient's age, gender or body weight. These were in contrast to other available NOACs, which were taken twice a day and needed dose adjustment for age and body weight.

The Xarelto SPC stated that 'The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. In the pivotal double-blind [Patel *et al*] study, 14,264 patients were assigned either to Xarelto 20mg once-daily (15mg once-daily in patients with creatinine clearance 30 - 49ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months'.

'Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 – 0.96; p<0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 – 1.03; p<0.001 for non-inferiority; p=0.117 for superiority)'.

The Xarelto SPC stated that there was no dose adjustment for the elderly population or for body weight or gender.

The Elequis SPC stated that a dose reduction was required if at least two of the following characteristics were present: age ≥80 years, body weight ≤60kg, or serum creatinine ≥1.5mg/dl (133micromole/l).

The Pradaxa SPC recommend close clinical surveillance in patients with a body weight <50kg. Xarelto was simple to use. The Panel had ruled on this general point in Case AUTH/2537/10/12. The claims on page 5 were in line with both the SPC and CHMP opinion. Consequently they could be substantiated and were therefore not in breach of the Code.

PANEL RULING

The Panel noted its comments at point B1 above regarding the citation of specific clauses in the complaint and considered that they applied here.

The Panel noted that page 5 was headed 'Simplicity matters' and sub-headed in emboldened text, 'A once-daily novel oral anticoagulant that provides 24hr protection …'. The sub-heading continued further down the page with '… without the need to adjust dose for a patient's age, gender or body weight' which was similarly emboldened. There then followed a description of the dosage regimen; one 20mg tablet once-daily (with food) for patients with atrial fibrillation and one 15mg tablet once-daily (with food) for atrial fibrillation patients with moderate or severe renal impairment. The Panel noted that the heading 'Simplicity matters' was on a page which clearly dealt with the once-daily dosing regimen of Xarelto. The Panel considered that the intended audience (nurses, payors, pharmacists and physicians) would be well acquainted with the complexities of treating patients with warfarin. The dosing regimen and monitoring of Xarelto patients was not as complicated as warfarin therapy. In the Panel's view, health professionals would know that with any anticoagulant, the risk of unintended bleeding had to be balanced against stroke prevention. The Panel did not consider that 'Simplicity matters' underplayed the complexity of anticoagulant therapy as alleged. No breach of Clause 7.9 was ruled. The Panel also ruled no breach of Clause 9.1.

With regard to the claim 'Once-daily Xarelto provides fast-acting, 24 hour protection', the Panel noted its comments at point A1 above. The Panel considered that, contrary to Bayer's submission, the claim implied that Xarelto had been shown to have a fast and measurable effect on the prevention of stroke and systemic embolism. In the Panel's view this was not so. The Panel thus considered that the claim was exaggerated as alleged. A breach of Clause 7.10 was ruled. The Panel further considered that the claim could not be substantiated and a breach of Clause 7.4 was ruled.

3 'Compliance matters'

This statement appeared as a heading to page 6.

COMPLAINT

Bristol-Myers Squibb and Pfizer noted that the sub-heading to page 6 was, 'Once-daily dosing improves

compliance ...'. Bristol-Myers Squibb and Pfizer submitted that the page was misleading and could imply that once-daily NOACs (such as Xarelto) offered improved compliance vs twice-daily NOACs (such as Bristol-Myers Squibb /Pfizer's Eliquis).

A disclaimer stated 'Not based on Xarelto data'. This page was referenced to Coleman *et al* (2012) which evaluated adherence rates of chronic cardiovascular therapy based on three criteria (taking adherence, regimen adherence, timing adherence). However, Bayer had chosen to use the timing adherence results only, where the difference between once-daily and twice-daily dosing was the largest. The other two adherence results were not included on the page, and therefore this data had been generalised implying that these results referred to overall treatment adherence. Furthermore, Coleman *et al* indicated several limitations to their analysis such as inclusion of studies of small sample size, populations with differing cardiovascular disease states resulting in statistical heterogeneity, publication bias, and exclusion of studies with missing information that the authors were unable to obtain following request.

In summary, Bristol-Myers Squibb and Pfizer considered that the claim 'Once-daily dosing improves compliance...' (by implication compared with the competitor NOACs which were twice-daily) could [sic] be substantiated and therefore should not be used.

In an inter-company letter Pfizer alleged a breach of Clauses 7.2, 7.4 and 9.1.

In their complaint to the Authority, Bristol Myers Squibb and Pfizer summarised their concerns about the booklet as a whole and referred to: Clause 7.2 (misleading by 'cherry picking' favourable data); Clause 7.4 (claims not capable of substantiation); Clause 7.9 (safety claims not capable of substantiation and safety underplayed); Clause 7.10 (exaggerated and all-embracing claims) and Clause 9.1 (high standards not maintained).

RESPONSE

Bayer noted that Pfizer and Bristol-Myers Squibb had made some very general comments about page 6, however there were no specific clauses cited so Bayer could not respond to any specific allegations.

Bayer stated that it appeared that Pfizer and Bristol-Myers Squibb regarded the page as a comparison of once-daily Xarelto and twice-daily Eliquis.

Bayer stated that it had not made any comparison with other NOACs on page 6. The comparison to Eliquis was an assumption by Pfizer and Bristol-Myers Squibb. This section clearly stated that once a day improved compliance and this could be substantiated by many publications including research supported by Pfizer and Bristol-Myers Squibb.

Literature review and meta-analysis supported by Pfizer and Bristol-Myers Squibb and published in Patient Preference Adherence, in May 2013 concluded that 'Current meta-analyses suggested that across acute and chronic disease states, reducing dosage frequency from multiple dosing to [once-daily] dosing may improve adherence to therapies among patients. Improving adherence may result in subsequent decreases in health care costs' (Srivastava *et al* 2013).

Renda and Caterina (2013) evaluated NOACs in atrial fibrillation and concluded, 'Indeed, a new oral anticoagulant that is proven to be effective and safe with a once-daily dosing is usually advantageous over other agents that need two administrations per day, with respect to drug adherence and patients' as well as physicians' acceptance'.

The EMA in its assessment report for Xarelto (22 September 2011 ref EMA/CHMP/301607/2011), under the section 'Final dose regimen chosen' accepted the argument of selection of a once a day dose based on phase II data and the advantage of patient convenience and compliance, 'In the phase II dose-finding studies, there was no dose response relationship or clear efficacy advantage observed for [twice-daily] dosing compared with [once-daily] dosing over the range of rivaroxaban doses tested, and no definitive difference between the [twice-daily] and [once-daily] regimens was seen in bleeding compared to [low molecular weight heparin-vitamin K antagonist], except at 40mg [three times a day] or higher. The [once-daily] dosing was considered advantageous from a patient convenience and compliance perspective'.

Bayer did not agree with Pfizer and Bristol-Myers Squibb's concern regarding Coleman *et al* and selection of timing adherence. Bayer noted that the authors mentioned that this was the first systematic review and meta-analysis published in literature to evaluate the effect of dosing frequency on chronic medication adherence and included prospectively collected data of 18 randomised clinical trials and 11 observational studies. The systematic review included clinical trials on anticoagulants. Adherence was measured by three definitions; taking adherence, regimen adherence and timing adherence. All definitions showed that that adherence was significantly improved by once-daily dosing ($p<0.01$ for all definitions of adherence). Bayer quoted from the publication 'Lastly, the percentage of near optimal inter-administration intervals was defined as timing adherence, which was the most stringent definition of adherence commonly used in the medical literature'.

Coleman *et al* also referred to the fact that simplifying the regimen with less frequent daily dosing seemed to be a reasonable intervention.

A similar recommendation was made by NICE in Medicine Adherence CG 76 with a suggested intervention of simplifying the dosing regimen.

The National Council on Patient Information and Education stated in its guidance, Enhancing Prescription Medicine Adherence: A National Action Plan, 'For many patients, one of the biggest

stumbling blocks to taking their medicines is the complexity of the regimen. Studies found that patients on once-daily regimens were much more likely to comply than patients who were required to take their medicine(s) multiple times each day'.

PANEL RULING

The Panel noted its comments at point B1 above regarding the citation of specific clauses in the complaint and considered that they applied here.

The Panel noted that page 6 was headed 'Compliance matters' and sub-headed 'Once-daily dosing improves compliance ...'. This was followed by a chart which showed that 76.3% of patients complied with once-daily dosing vs 50.4% with twice-daily dosing. A highlighted box to the right-hand side of the chart featured the claim '25% increase in treatment adherence in once-daily vs twice-daily regimens'. The chart and claim were based on the results of Coleman *et al*, a pooled analysis of 29 studies of patients taking chronic cardiovascular therapy including anticoagulants. The x axis of the chart was labelled 'Dosing frequency – Not based on Xarelto data'. In the Panel's view, given the context in which it appeared, the chart implied that it had been unequivocally shown that 76.3% of patients would comply with once-daily Xarelto therapy vs 50.4% of patients taking a twice-daily alternative. This was not so; the Panel considered that such an implication was misleading and could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

4 'When it really matters'

This statement appeared as the heading to page 8.

COMPLAINT

Bristol-Myers Squibb and Pfizer noted the claim 'Xarelto provides simple, proven, predictable anticoagulation for stroke prevention in non-valvular AF'. As stated above, 'simple' in that context inferred an all-embracing general claim and suggested that Xarelto was simple to use. Bristol-Myers Squibb and Pfizer submitted that this underplayed the complexity of anticoagulation treatment. In an inter-company letter Pfizer alleged breaches of Clauses 7.9 and 9.1.

Furthermore, the page demonstrated further 'cherry picking' of positive (superior vs warfarin) secondary endpoints with omission of important and relevant safety endpoints as mentioned above. It mentioned protection against stroke and systemic embolism but did not state this was non-inferior to warfarin which was the primary endpoint of the study or that major bleeding was non-inferior to warfarin. In an inter-company letter Pfizer alleged a breach of Clauses 7.2 and 9.1.

In their complaint to the Authority, Bristol Myers Squibb and Pfizer summarised their concerns about the booklet as a whole and referred to: Clause 7.2 (misleading by 'cherry picking' favourable data); Clause 7.4 (claims not capable of substantiation); Clause 7.9 (safety claims not capable of substantiation and safety underplayed); Clause 7.10 (exaggerated and all-embracing claims) and Clause 9.1 (high standards not maintained).

Given its concerns, Bristol-Myers Squibb and Pfizer submitted that use of the above claims should cease in all Xarelto materials exhibited at meetings, in all Xarelto advertising, and in any Xarelto promotional materials currently being used by Bayer colleagues.

RESPONSE

Bayer noted that Pfizer and Bristol-Myers Squibb had discussed a number of points but had not specified any particular clause of the Code in relation to their concerns. The complainants had discussed the claim that 'Xarelto provides simple, proven, predictable anticoagulation ...'. Prior to the introduction of this latest class of anticoagulants, there were two main treatment options. These were injectable anticoagulants such as heparin and oral vitamin K antagonists like warfarin.

Heparins required dose adjustment by weight and needed to be administered at least once a day. Injections might result in extensive bruising, stress of needle prick, pain and discomfort. Self-injection called for dexterity which not all older patients had, if this was the case help from a carer or visit by a district nurse was necessary. In addition, sharps and needles had to be disposed of properly.

Vitamin K antagonists had a number of limitations including a narrow therapeutic index which required monitoring of the international normalised ratio (INR) and adjustment of the dose accordingly. There were three tablet strengths (1mg, 3mg, 5mg) which had to be used in various combinations in order to administer the required dose. This could be a source of dose error. This point was made in the Rapid Response Report NPSA/2010/RRR018, 'Preventing fatalities from medication loading doses'. Table 2 in the report 'Medication involved in reported incidents' listed warfarin as the first of four critical medicines linked to loading dose errors.

The dose of warfarin needed to be adjusted to take account of changes in food, drinks and concomitant medications. Travelling and holidays might also be a concern and the majority of patients who had to attend clinics regularly for monitoring might find it difficult. Such considerations had an impact on lifestyle.

Considering this background of anticoagulation, NOACs were simple to use and Xarelto with a once-daily, simple regimen was convenient and easy to use. Bayer cited the fact that the CHMP, the Atrial Fibrillation Association (patient organisation), the European Society of Cardiology and clinicians with an interest in anticoagulation considered that the class of medicine to which Xarelto belonged was easier to manage, offered convenience and was simple.

PANEL RULING

The Panel noted its comments at point B1 above regarding the citation of specific clauses in the complaint and considered that they applied here.

The Panel noted that page 8 was headed 'When it really matters' followed by the sub-heading 'Xarelto provides simple, proven, predictable anticoagulation for stroke prevention in non-valvular AF'. The first bullet point 'Simplicity matters' referred to the once-daily dosage with no adjustment needed for age, gender or body weight. The Panel noted its comments at point B2 above and considered that they applied here. The Panel did not consider that 'simple' was an all-embracing claim as alleged; it was clearly linked to the Xarelto dosage regimen details of which appeared immediately beneath. No breach of Clause 7.9 was ruled. The Panel also ruled no breach of Clause 9.1.

The Panel noted the general allegation of 'cherry picking' of positive data for Xarelto vs warfarin and the omission of important and relevant safety endpoints. The Panel considered that the presentation of positive data without reference to endpoints where Xarelto was 'non-inferior' to warfarin was not necessarily unacceptable. In the Panel's view page 8 did not imply that Xarelto was more efficacious than warfarin; it highlighted some areas where Xarelto had a better safety profile vs warfarin and it referred to the dosage regimen of Xarelto. The Panel, however, noted its comments at point B1 above about the increased risk of bleeding from GI sites with Xarelto vs warfarin. The bullet point on page 8 entitled 'Safety profile matters' referred to the decreased risk of fatal bleeds and of devastating inter-cranial haemorrhage with Xarelto vs warfarin but not to the increased risk of bleeding from GI sites. In the Panel's view, although Patel *et al* had shown that overall Xarelto had a comparable safety profile compared with warfarin, it was important for health professionals to know that patients treated with Xarelto were at increased risk of GI bleeds vs patients on warfarin; the health professionals could thus manage that risk appropriately. The Panel considered that page 8 was misleading in that regard and a breach of Clause 7.2 was ruled. The Panel also ruled a breach of Clause 9.1.

Complaint received **1 November 2013**

Case completed **4 February 2014**

HEALTH PROFESSIONAL v MERCK SHARP & DOHME

Alleged promotion of unlicensed medicines

An anonymous, non-contactable health professional alleged that Merck Sharp & Dohme had promoted unlicensed medicines at a meeting of the European Society of Gynaecological Oncology (ESGO) in Liverpool 2013.

The complainant stated that he/she understood that a medicine could not be promoted before the grant of a marketing authorization but that certain limited activities could take place eg legitimate scientific exchange or responding to an unsolicited request for information. At the Merck Sharp & Dohme stand at ESGO there were large exhibition panels which advertised the company's pipeline products eg Programmed Death–1 (PD-1) Inhibitor, Cyclin Dependent Kinase (CDK) Inhibitor and Extracellular Signal – Regulated Kinase (ERK) Inhibitor and their mode of actions and on-going trials. The complainant queried how this was legitimate exchange as it was on an exhibition panel. The complainant considered that this was the company getting delegates to ask about the products - in his/her view this was not unsolicited.

The complainant was not aware that any of these products were licensed anywhere and whilst it was important that health professionals were kept up-to-date on developments and trial options for patients, he/she considered that the health professionals should review the data themselves and discuss with clinical research and medical at the companies; they should not be faced with what looked like promotional panels for medicines which had not had their efficacy and safety evaluated. There were patient groups and potentially carers present at such conferences these days and they would inevitably ask for these new compounds. The complainant alleged that such activity was misleading and promoting before the grant of a licence.

The detailed response from Merck Sharp & Dohme is given below.

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

The Panel noted that the Code prohibited the promotion of a medicine prior to the grant of its marketing authorization. It also required that promotion must be in accordance with the marketing authorization and not be inconsistent with the summary of product characteristics (SPC). The supplementary information provided additional details, including that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that this did not constitute promotion which was prohibited.

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

The Panel noted that the PMCPA Guidance about Clause 3 included advice about the legitimate exchange of medical and scientific information during the development of a medicine. Companies must ensure that such activities constituted a genuine exchange of information and were not promotional. Documents must not have the appearance of promotional material. It should be borne in mind that it would be a breach of the Code if non-promotional information on products or indications that were not licensed was used for a promotional purpose.

The Panel did not consider that the arrangements for the exhibition stand at issue could take the benefit of the exemption to the definition of promotion for unsolicited enquiries. It noted that Merck Sharp & Dohme held a company sponsored satellite symposium. There was no complaint about the satellite symposium and the Panel had no information about it. The Panel was only considering the exhibition stand.

The Panel examined the information on the 6 exhibition stand posters. Three of them referred to particular inhibitors ERK, PD-1 and CDK. Each was illustrated with a diagram of cell activity. This was followed by a description of the pathway or molecule. The final part of each of these three posters referred to the Merck Sharp & Dohme product under development and the final statement 'The agent or uses depicted are investigational'. The PD-1 poster referred to in vivo and *in vitro* data which showed the effect of blockade. The fourth poster (exhibition stand panel 6) gave details about the PROCEED trial which was a phase 3 trial of vintafolide in platinum-resistant ovarian cancer. At the bottom of the poster was an invitation 'to learn more'. This mentioned the availability of additional information as well as how to find out how to participate in the trial by speaking to the representative on the booth or calling a US/international number or visiting clinicaltrials.gov. The fifth poster depicted the Merck Sharp & Dohme oncology research pipeline giving details of the investigational compound and description of the target. Again, the phrase 'The agents or

uses depicted here have not been approved by any regulatory agency' appeared. The final poster was a Merck Sharp & Dohme oncology corporate poster. It had no reference to products.

The Panel noted the research phase of each product and its licensing status. Only one of the molecules referred to on the exhibition stand had been submitted to any regulatory agency around the world. When the ESGO meeting was held, any regulatory approval, if granted, was estimated to be some time away, and was still speculative.

The Panel considered that relevant factors for consideration in such circumstances included the nature of the meeting, the status of attendees, the location of the Merck Sharp & Dohme stand and whether it constituted the legitimate exchange of medical and scientific information during the development of a medicine.

The Panel noted Merck Sharp & Dohme's submission that the ESGO meeting was a meeting of high scientific standing and attendees would include researchers etc.

The Panel noted that the posters primarily detailed the effect of the target for the investigational compounds, the PD1 poster, however, was slightly different as was the poster describing the PROCEED trial. The Panel noted Merck Sharp & Dohme's submission that it had not promoted any of its licensed products on the exhibition stand. Merck Sharp & Dohme referred to the products as investigational molecules/agents. Whilst this term was not defined, the Panel queried whether products subject to Phase III trials (vintafolide and MK3475) and for which a licence was anticipated within a year would be considered investigational molecules.

The Panel considered that delegates were likely to view the exhibition space as a whole as promotional and might not necessarily appreciate the differences between promoting products and promoting research. The Panel noted Merck Sharp & Dohme's submission that the exhibition hall was used as part of the scientific programme as it hosted the ESGO poster display area.

The Panel considered that it was difficult to decide whether the materials were in line with the requirements of the supplementary information to the Code. It noted that one of Merck Sharp & Dohme's aims was to raise awareness of the company's commitment to oncology and to talk with basic and clinical scientists. The company also wanted to make clinicians aware of the ongoing Phase III clinical trial. The Panel noted that the style of the posters was low key and scientific. The stand was manned by scientific and medical staff. Only one of the products had been submitted for approval but this was not expected for some time.

The Panel did not know whether the meeting agenda included any content that could be considered the legitimate exchange of medical and scientific information during the development of the Merck Sharp & Dohme products. Merck Sharp & Dohme had sponsored a satellite symposium but there was no complaint about that and the Panel had no information about it.

The Panel was only concerned about the PD-1 poster and the PROCEED trial poster. The PROCEED trial poster in particular was materially different to the other posters both in content and the licensing status of the product. The poster advised delegates that the trial was currently recruiting and was thus an invitation to participate. In the Panel's view the invitation would necessarily solicit enquiries. The Panel queried whether any associated discussion about the logistics of trial participation and the provision of information about the medicine in relation to the trial could fairly be described as the legitimate exchange of medical and scientific information. The Panel however had no evidence before it about such discussions. Given the discrete nature of such discussions the Panel queried whether it was appropriate to display the PROCEED trial poster alongside the others.

The Panel considered that the other four posters did not constitute advertising a product prior to the grant of the marketing authorization. There was very limited information about the efficacy of any potential product on these four posters and the products were a long way from receiving any licence. Similarly, whilst the Panel was concerned about the in vivo and *in vitro* data in the PD1 poster it was, nonetheless, limited and on balance the Panel did not consider that it was advertising a product prior to the grant of its marketing authorisation. No breach was ruled in relation to the five posters.

The Panel noted its concerns about the PROCEED trial poster set out above. The Panel considered that within the context of the exhibition stand it did not satisfy the requirements for the legitimate exchange of medical and scientific information during the development of a medicine. Nevertheless, given the narrow grounds of the complaint and on balance, the Panel did not consider that the poster amounted to the promotion of an unlicensed medicine and no breach was ruled.

The Panel noted the allegation that the Merck Sharp & Dohme stand would encourage requests for the new products as patient groups and carers might be present at the meeting. It did not appear that the meeting was aimed at such an audience and the data provided by Merck Sharp & Dohme in relation to the attendees at the 2011 meeting did not mention patient groups or carers. The Panel considered that the complainant had not discharged his/her burden of proof and thus ruled no breach including Clause 2.

An anonymous, non-contactable health professional alleged that Merck Sharp & Dohme Limited had promoted unlicensed medicines at a meeting of the European Society of Gynaecological Oncology (ESGO) in Liverpool, 19-22 October, 2013.

COMPLAINT

The complainant stated that he/she understood from the Code that a medicine could not be promoted before the grant of a marketing authorization but that certain limited activities could take place eg legitimate scientific exchange or responding to an unsolicited request for information. At the Merck Sharp & Dohme stand at ESGO there were large exhibition panels which advertised the company's pipeline products eg Programmed Death–1 (PD-1) Inhibitor, Cyclin Dependent Kinase (CDK) Inhibitor and Extracellular Signal – Regulated Kinase (ERK) Inhibitor and their mode of actions and on-going trials. The complainant queried how this was legitimate exchange as it was on an exhibition panel. The complainant considered that this was the company getting delegates to ask about the products - in his/her view this was not unsolicited.

The complainant was not aware that any of these products were licensed anywhere else in the world outside of the UK and whilst it was important that health professionals were kept up-to-date on developments and trial options for patients, he/she considered that the health professionals should review the data themselves and discuss with clinical research and medical at the companies; they should not be faced with what looked like promotional panels for medicines which had not had their efficacy and safety evaluated. There were patient groups and potentially carers present at such conferences these days and they would inevitably ask for these new compounds when they saw such materials as these. The complainant alleged that such activity was misleading and promoted before the grant of a licence.

When writing to Merck Sharp & Dohme the Authority asked it to bear in mind Clauses 2, 3.1, 9.1, 22.1 and 22.2 of the Code.

RESPONSE

Merck Sharp & Dohme explained that oncology was a highly specialized therapeutic area. The science was fast moving and constantly changed as new data emerged. The design of studies was complex and interpretation of the data was challenging. The data were often preliminary and incomplete. There was a constant focus by the clinical community on minimizing the number of patients exposed to potential harm and maximizing the therapeutic opportunity. The time window for clinical intervention was often limited by disease progression. The clinical community challenged researchers to share data at the earliest appropriate time.

The meeting in question was the 18th International Meeting of ESGO, a biennial meeting of high scientific standing. The ESGO website stated that:

> 'Each ESGO meeting offers attendees many opportunities for the dissemination, discussion and debate of the updated medical and scientific information for gynaecological cancer treatment and care.'
>
> 'More than 2500 gynaecological oncologists, researchers, residents and students will be gathering for the 18th International Meeting of the European Society of Gynaecological Oncology. Join your colleagues and take part in an extraordinary educational forum, where you will learn about the latest development, techniques and practices from world renowned speakers on all the latest topics.'

Merck Sharp & Dohme submitted that its global oncology team decided to support the meeting based on the highly specialist and research oriented nature of the gynaecological oncologists who would attend. The company's objectives in participating in this meeting were:

- To raise awareness of Merck Sharp & Dohme's commitment to oncology – the company made a significant investment in basic and clinical research into novel oncology targets but was not currently known as a major oncology company. The purpose of this awareness raising included things such as generating collaborative research opportunities, licensing opportunities and bidirectional scientific dialogue. Only by talking with basic and clinical scientists could the company and scientists make progress together.
- To share with the clinical community the novel biological pathways that Merck Sharp & Dohme targeted with its research. Some of these targets were currently thought to be relevant to the gynae-oncology community, others less so. As was common in oncology, many of these would not result in effective medicines but through this research the company's understanding of cancer biology would advance incrementally.
- To make clinicians aware of a clinical trial in platinum-resistant ovarian cancer which was currently recruiting patients in Europe. This was an area of unmet need with limited options available for patients, where clinicians wanted to know what trials were available for their patients. In the UK, it was a stated goal of the NHS that more patients were recruited into research.

Merck Sharp & Dohme had a presence in the exhibition hall and sponsored a satellite symposium entitled 'Recurrent Ovarian Cancer: Is Personalized Medicine a Reality for Patients?'. The meeting attracted around 2,500 delegates who specialized in medical oncology (who generally acted as investigators in clinical trials), clinical oncology, gynaecological surgery, and researchers in the field of gynaecological oncology. Merck Sharp & Dohme submitted that the meeting was highly scientific and was therefore an appropriate setting for genuine scientific exchange between the pharmaceutical industry, academic researchers and health professionals to occur. Pharmaceutical companies, medical device companies, diagnostic companies, the medical press and professional societies such as ESGO and the International Gynaecologic Cancer Society (IGCS) exhibited at the meeting.

The exhibition hall was used as part of the scientific programme as it hosted the poster display area. A diagram showing the hall layout was provided.

Merck Sharp & Dohme stated that its exhibition space was not used to promote any products. It comprised an unbranded medical and scientific affairs stand, and was intended to demonstrate the company's commitment to the development of new oncology therapies. Conscious of the challenges posed in combining scientific discussions with promotional activities at the same venue, Merck Sharp & Dohme decided not to have any material or promotion related to its licensed oncology and women's health products which could have been promoted, but which were not. Likewise, the company decided to focus on the science - mechanisms and biological pathways, biomarkers etc. - rather than present clinical efficacy or safety data, where it existed, and to staff the stand with appropriately trained scientific and medical staff. The stand was staffed exclusively by members of the medical affairs team during the meeting; it was never manned by members of sales or marketing and no sales people attended at the congress.

The stand was manned fulltime by a pharmacist employed as a medical information and product specialist who had extensive experience in handling scientific enquiries from health professionals. She was supported during breaks by an oncology medical science liaison (MSL). The MSL role was a non promotional, field-based medical affairs employee responsible for a therapeutic area such as oncology. Also present at times, and as delegates at the meeting, were two Merck Sharp & Dohme oncology physicians, one from oncology medical affairs, Germany and the other responsible for oncology medical affairs in Europe. As experienced medical affairs employees, no written briefing was given specific to this congress. A verbal briefing was given by the UK oncology medical adviser and UK medical information product specialist to the international Merck Sharp & Dohme medical affairs attendees. The key points of the briefing were:

- the requirements under the Code, as the meeting was an international congress which took place in the UK
- that promotion of unlicensed medicines was not allowed
- that staff were to respond to enquiries reactively, not to initiate discussion
- that there should be no proactive discussion of licensing status or possible timelines of regulatory milestones
- that staff should ensure all enquiries were logged, and subsequently passed to the scientific service for the Merck Sharp & Dohme affiliate in the country of the enquirer.

Merck Sharp & Dohme summarized the contents of the exhibition panels:

- panel 1: 'Merck Sharp & Dohme Oncology' panel highlighted the company's commitment to patients – image and slogan
- panels 2- 5: The panels highlighted the novel mechanisms and biological targets in development in the company's oncology pipeline. There was no detail of the tumour types studied. There were no statements on the panels about efficacy or adverse event profiles, nor was there any comparisons with any other oncology treatments. The panel made clear that the molecules were investigational
- panel 6: This panel summarized the design of a phase III study currently recruiting in Europe, including the UK, for patients with platinum-resistant ovarian cancer.

No materials were available on the stand for attendees and there was no invitation that 'more information is available on request'.

Merck Sharp & Dohme submitted that the exhibition panels were examined before the meeting by the oncology medical adviser and director of medical affairs as this exhibition was regarded as a non-promotional activity. The UK medical adviser had been trained extensively on the Code, including an exit assessment. Merck Sharp & Dohme provided details of its training programme. The UK MSLs and medical advisers received additional training on the guidance on Clause 3 of the Code in quarter 2 2013.

The UK medical affairs department working practice document articulated the company's guiding principles. The process for management of medical information stands at global congresses was described in a global SOP.

Merck Sharp & Dohme stated that the molecules mentioned on the panels were all in early phase research. The ERK inhibitor and HDM2 inhibitor were both in Phase I. MK3475 was being studied across various tumour types in Phase I to III. Phase III studies in melanoma and non-small cell (NSC) lung cancer started shortly after this congress took place. Vintafolide was in Phase II for non-small cell lung cancer and Phase III for ovarian cancer.

None of the molecules displayed on the stand panels had been submitted to any regulatory agency around the world, with the exception of vintafolide. Vintafolide had been submitted to the European Medicines Agency (EMA). When the ESGO meeting was held, regulatory approval, if granted, was estimated to be at least six to nine months away, and was still speculative.

The next molecule likely to become available was MK3475, assuming the studies confirmed the preliminary data. The other molecules were further from regulatory review.

None of these investigational agents were available for clinical use outside clinical trials – no compassionate use, expanded access or named patient programmes.

Merck Sharp & Dohme submitted that its activities at ESGO represented the legitimate exchange of medical and scientific information during the

development of a medicine, as permitted by the Code. The company did not consider that its activities could be interpreted as promotion of a medicine prior to the grant of a marketing authorization.

- none of the products were available to prescribe, outside the clinical trial setting
- the ESGO congress was an international congress of high scientific standing appropriate to the legitimate exchange of medical and scientific information
- there was no mention on the exhibition panels of any potential indication or specific tumour type, except when describing a clinical trial for which patients may be referred
- it was clearly stated that all agents were investigational
- no data were presented or claims made regarding efficacy or safety
- there were no details provided of regulatory timelines
- the activity was staffed solely and reactively by appropriately trained and experienced scientific staff, based within the company's medical function.

For these reasons, Merck Sharp & Dohme submitted that these activities did not amount to a breach of Clause 3.1.

Merck Sharp & Dohme submitted that, as described above, the primary purpose of the ESGO meeting was scientific, directed at a highly specialised group of clinical and research professionals. There was no evidence that members of the public attended the scientific meeting itself nor was there provision for patients to register as delegates. The ESGO Sponsorship and Exhibition Prospectus provided a detailed breakdown of delegates who attended the 2011 ESGO in Milan and there was no mention of patient groups or members of the public registering as delegates. The professional expertise listed were obstetrics & gynaecology (56%), oncology (34%), radiation oncology (4%), molecular cell biology (2%), pathology (2%), internal medicine (1%) and radiology/imaging (1%) which accounted for 100% of the delegates.

Merck Sharp & Dohme submitted therefore that the exhibition and poster area were primarily intended for clinicians, scientists and researchers and not for members of the public or patients. In any event, the activity on Merck Sharp & Dohme's stand was not promotional, and could not constitute promotion to the public.

Merck Sharp & Dohme submitted that Clauses 22.1 or 22.2 had not been breached.

Merck Sharp & Dohme denied breaches of Clauses 3.1, 22.1 and 22.2. Indeed, the company submitted that it had been particularly careful to maintain high standards of scientific exchange and that, far from bringing discredit upon the industry, this type of activity, carefully planned and executed, was an essential part of academic engagement that enhanced collaboration during the development of medicines, for the ultimate benefit of cancer patients.

Merck Sharp & Dohme thus denied breaches of Clauses 9.1 and 2.

In summary, Merck Sharp & Dohme stated that its stand at the ESGO meeting was scientific in nature and demonstrated to the healthcare community that the company was committed to develop new oncology therapies. The stand was manned at all times by experienced medical affairs staff, not by promotional staff members, and was intended for the legitimate scientific exchange at a meeting which was scientific by its very nature. There were no claims on the exhibition panels about efficacy or safety of any of the molecules. No materials were provided on the stand. Merck Sharp & Dohme strongly rejected the claims that it had promoted a medicine prior to a marketing authorization or that it advertised a prescription medicine to members of the public.

PANEL RULING

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

The Panel noted that Clause 3 prohibited the promotion of a medicine prior to the grant of its marketing authorization. It also required that promotion must be in accordance with the marketing authorization and not be inconsistent with the summary of product characteristics (SPC). The supplementary information to Clause 3 provided additional details, including a clear statement that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that this did not constitute promotion which was prohibited by Clause 3 or any other clause in the Code.

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

The Panel noted that the PMCPA Guidance about Clause 3 included advice about the legitimate exchange of medical and scientific information during the development of a medicine. This was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under this or any other clause. Companies must ensure that such activities constituted a genuine exchange of information and were not promotional. Documents must not have

the appearance of promotional material. It should be borne in mind that it would be a breach of the Code if non-promotional information on products or indications that were not licensed was used for a promotional purpose.

The Panel did not consider that the arrangements could take the benefit of the exemption to the definition of promotion for unsolicited enquiries. It noted that Merck Sharp & Dohme held a company sponsored satellite symposium in addition to the exhibition stand at issue. There was no complaint about the satellite symposium and the Panel had no information about it. The Panel was only considering the exhibition stand.

The Panel examined the information on the 6 exhibition stand posters. Three of them referred to particular inhibitors ERK, PD-1 and CDK. Each was illustrated with a diagram of cell activity. This was followed by a description of the pathway or molecule. The final part of each of these three posters referred to the Merck Sharp & Dohme product under development and the final statement 'The agent or uses depicted are investigational'. The PD-1 poster referred to *in vivo* and *in vitro* data which showed that PD1 and/or PD-L1 blockade using monoclonal antibodies enhanced tumour cell-specific T-cell activation, cytokcine production, anti-tumour effector mechanisms, and clearance of tumour cells by the immune system. The fourth poster (exhibition stand panel 6) gave details about the PROCEED trial which was a phase 3 trial of vintafolide in platinum-resistant ovarian cancer. It was headed 'Now enrolling patients with platinum-resistant ovarian cancer'. It stated that vintafolide was a conjugate of folate linked to a named chemotherapy agent which was being used in conjunction with etarfolatide to identify patients with tumors that expressed folate receptors. The poster gave details about the study design, outcome measurements as well as the inclusion and exclusion criteria. At the bottom of the poster was an invitation 'to learn more'. This mentioned the availability of additional information as well as how to find out how to participate in the trial by speaking to the representative on the booth or calling a US/international number or visiting clinicaltrials.gov. The fifth poster depicted the Merck Sharp & Dohme oncology research pipeline giving details of the investigational compound and description of the target. Again, the phrase 'The agents or uses depicted here have not been approved by any regulatory agency' appeared. The final poster was a Merck Sharp & Dohme oncology corporate poster. It had no reference to products.

The Panel noted the research phase of each product. The ERK inhibitor and HDM2 inhibitor were both in Phase I. MK3475 was being studied across various tumour types in Phase I to III. Phase III studies in melanoma and non-small cell (NSC) lung cancer started shortly after this congress took place. Vintafolide was in Phase II for non-small cell lung cancer and Phase III for ovarian cancer.

The Panel also noted each product's licensing status. Only one of the molecules referred to on the exhibition stand had been submitted to any regulatory agency around the world. Vintafolide had been submitted to the European Medicines Agency (EMA) for conditional approval for the treatment of platinum-resistant ovarian cancer based on preliminary phase II data. When the ESGO meeting was held, regulatory approval, if granted, was estimated to be at least six to nine months away, and was still speculative.

The Panel considered that relevant factors for consideration in such circumstances included the nature of the meeting, the status of attendees, the location of the Merck Sharp & Dohme stand and whether it constituted the legitimate exchange of medical and scientific information during the development of a medicine.

The Panel noted Merck Sharp & Dohme's submission that the ESGO meeting was a meeting of high scientific standing and attendees would include researchers etc.

The Panel noted that the posters primarily detailed the effect of the target for the investigational compounds, the PD1 poster, however, was slightly different as was the poster describing the PROCEED trial. The Panel noted Merck Sharp & Dohme's submission that it had not promoted any of its licensed products on the exhibition stand. Merck Sharp & Dohme referred to the products as investigational molecules/agents. Whilst this term was not defined, the Panel queried whether products subject to Phase III trials (vintafolide and MK3475) and for which a conditional licence was anticipated within 12 months (vintafolide) would be considered investigational molecules.

The Panel considered that delegates were likely to view the exhibition space as a whole as promotional and might not necessarily appreciate the differences between promoting products and promoting research. The Panel noted Merck Sharp & Dohme's submission that the exhibition hall was used as part of the scientific programme as it hosted the ESGO poster display area.

The Panel considered that it was difficult to decide whether the materials were in line with the requirements of the supplementary information to Clause 3. It noted that one of Merck Sharp & Dohme's aims was to raise awareness of the company's commitment to oncology and to talk with basic and clinical scientists. The company also wanted to make clinicians aware of the ongoing Phase III clinical trial. The Panel noted that the style of the posters was low key and scientific. The stand was manned by scientific and medical staff. Only one of the products had been submitted for approval but this was not expected for at least six to nine months.

The Panel did not know whether the meeting agenda included any content that could be considered the legitimate exchange of medical and scientific information during the development of the Merck Sharp & Dohme products. Merck Sharp & Dohme had sponsored a satellite symposium but there

was no complaint about that and the Panel had no information about it.

The Panel was only concerned about the PD-1 poster and the PROCEED trial poster. The PROCEED trial poster in particular was materially different to the other posters both in content and the licensing status of the product. The poster advised delegates that the trial was currently recruiting and was thus an invitation to participate. In the Panel's view the invitation would necessarily solicit enquiries. The Panel queried whether any associated discussion about the logistics of trial participation and the provision of information about the medicine in relation to the trial could fairly be described as the legitimate exchange of medical and scientific information. The Panel however had no evidence before it about such discussions. Given the discrete nature of such discussions the Panel queried whether it was appropriate to display the PROCEED trial poster alongside the others.

The Panel considered that the other four posters did not constitute advertising a product prior to the grant of the marketing authorization. There was very limited information about the efficacy of any potential product on these four posters and the products were a long way from receiving any licence. Similarly, whilst the Panel was concerned about the *in vivo* and *in vitro* data in the PD1 poster it was, nonetheless, limited and on balance the Panel did not consider that it was advertising a product prior to the grant of its marketing authorisation. No breach of Clause 3.1 was ruled in relation to the five posters.

The Panel noted its concerns about the PROCEED trial poster set out above. The Panel considered that within the context of the exhibition stand it did not satisfy the requirements for the legitimate exchange of medical and scientific information during the development of a medicine. Nevertheless, given the narrow grounds of the complaint and on balance, the Panel did not consider the poster amounted to the promotion of an unlicensed medicine and no breach of Clause 3.1 was ruled.

The Panel noted the allegation that the Merck Sharp & Dohme stand would encourage requests for the new products as patient groups and carers might be present at the meeting. It did not appear that the meeting was aimed at such an audience and the data provided by Merck Sharp & Dohme in relation to the attendees at the 2011 meeting did not mention patient groups or carers. The Panel considered that the complainant had not discharged his/her burden of proof and thus ruled no breach of Clause 22.1 and 22.2. Noting its rulings above the Panel ruled no breach of Clauses 2 and 9.1.

Complaint received **8 November 2013**

Case completed **11 December 2013**

CASE AUTH/2653/11/13

NOVO NORDISK v SANOFI

Provision of insufficient data from head-to-head study

Novo Nordisk complained about a Lyxumia (lixisenatide) presentation issued by Sanofi. Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as add-on therapy to achieve glycaemic control in adult type 2 diabetics otherwise inadequately controlled with oral glucose-lowering medicines and/or basal insulin together with diet and exercise. Novo Nordisk marketed Victoza (liraglutide) which was also a GLP-1 receptor agonist for use in type 2 diabetes.

Novo Nordisk referred to two slides. Slide 4 was headed 'New Lyxumia provides significantly greater reductions in PPG [post-prandial glucose] excursion and exposure compared with liraglutide'. This was followed by a graph headed 'Lyxumia 20mcg once-daily significantly reduced PPG excursion vs liraglutide 1.8mg once daily (p<0.0001)' referenced to Kapitza *et al* (2013). The graph showed mean change from pre-meal plasma glucose. The test meal was given 30 minutes after the medicine and the graph showed the data for every 30 minutes for 4.5 hours.

Slide 23 was headed 'Comparative effects on glucagon suppression' and featured a graph headed 'Lyxumia 20mcg once-daily provides a greater decrease in post-meal glucagon secretion than liraglutide 1.8mg once-daily' referenced to Kapitza *et al* and data on file. The graph compared mean plasma glucagon against theoretical time (0-4 hours 30 minutes). The final statement 'Glucagon AUC [area under curve] 0.30-4.30h (h-pg/mL) mean change from baseline. Estimated treatment difference – 21.2 p = 0.032' was referenced to data on file.

Novo Nordisk noted that the efficacy sections of both products' summaries of product characteristics (SPCs) presented the data for glycaemic control first (HbA_{1c} reductions, change in body weight and proportion of patients reaching the target of <7% HbA_{1c}). Novo Nordisk submitted that these were the three most recognised measures of diabetes/ glycaemic control used in clinical practice and by bodies such as the National Institute for Health and Care Excellence (NICE). Examples were given regarding the effect of hyperglycaemia as measured by updated mean HbA_{1c} and correcting post-meal hyperglycaemia.

The SPC efficacy sections for both products also showed results for changes in fasting plasma glucose (FPG), postprandial glucose (PPG) and body weight. In addition effects on beta cell function, cardiovascular evaluation and paediatric population were discussed.

Novo Nordisk submitted that the correct way to present and compare efficacy looking at PPG excursions of once-daily GLP-1 receptor agonists was to present the 24 hour PPG profile. Kapitza *et al* had published these data but Sanofi had not presented these results. The title of slide 4, 'New Lyxumia provides significantly greater reductions in PPG excursion and exposure compared with liraglutide', suggested that Lyxumia provided a greater reduction in PPG excursion than Victoza after every meal. Slide 4 failed to clarify that the claim was only true in respect of the test meal post-injection.

Kapitza *et al* showed that Victoza was superior (60% better) in the most clinically relevant measure of glucose control ie HbA_{1c} lowering efficacy. Sanofi did not provide these results in the presentation although at slide 8 HbA_{1c} efficacy data was used to show non-inferiority between Lyxumia and exenatide. This result was even more important considering Kapitza *et al* was the only head-to-head comparison of Victoza and Lyxumia. Novo Nordisk submitted that these results should thus not be ignored.

Another clinically relevant efficacy measure available from Kapitza *et al* was weight reduction. The study had shown that Victoza was superior to Lyxumia (50% better). Nevertheless, Sanofi did not present these results. Sanofi also did not refer to the fasting plasma glucose (FPG) data in the comparison of Lyxumia and Victoza when Victoza provided significantly greater reductions in FPG than Lyxumia.

Novo Nordisk alleged that Sanofi had used data from Kapitza *et al* very selectively to present Lyxumia more favourably. Clinically relevant results showing advantages for Victoza (24 hour glucose control, HbA_{1c} reductions and weight reductions) had been ignored while only results of less clinically relevant outcome measures with advantages for Lyxumia (PPG reductions after the test meal only and glucagon suppression) had been presented. Novo Nordisk alleged that this was misleading.

The response from Sanofi is detailed below.

The Panel noted that the presentation was entitled 'When it is time to add to basal insulin' followed by a reference to Lyxumia and 'A positive addition can make all the difference'. The next two slides were headed 'Choices to control PPG can be complex for patients on basal insulin' and 'Prandial GLP-1 receptor agonists have a greater effect on PPG than non-prandial agents'. The Panel noted that the presentation had been withdrawn following Case AUTH/2604/5/13. Sanofi stated that slides 4 and 23 remained unchanged and were still in use.

The presentation was designed, at least in part, to compare the clinical use of the available GLP-1 receptor agonists and the treatment choices

available in that regard for type 2 diabetics uncontrolled on existing treatment regimens. However, as Victoza was only licensed to be given in combination with oral antidiabetic medicines and not insulin, the Panel queried whether a comparison of Lyxumia with Victoza should have been included at all in a presentation entitled 'When it's time to add to basal insulin'. The comparative information about Lyxumia and Victoza was limited to PPG excursion (slide 4) and post-meal glucagon secretion (slide 23) data from Kapitza *et al* which was a pharmacodynamic comparison, and according to Novo Nordisk, the only direct comparison, of the two medicines.

The Panel noted Sanofi's submission that Kapitza *et al* was not a comparison of the efficacy of the two medicines as defined by overall glycaemic control. Sanofi had further submitted that the duration of the study (28 days) and the fact that mean HbA_{1c} was a secondary outcome in a study which was designed to measure short-term pharmacodynamic differences between Lyxumia and Victoza, meant that any differences noted between the two in terms of glycaemic control might not reflect clinical use. The authors stated that 'With respect to clinical reality, a limitation of this study is the relatively short observation time of 28 days. Indeed direct conclusions with regard to long-term metabolic control should not be made'. The Panel noted Novo Nordisk's submission that although Sanofi had not shown the HbA_{1c} efficacy data for Lyxumia vs Victoza (based on Kapitza *et al*), the company had included such data for Lyxumia vs exenatide. The Panel noted, however, that the Lyxumia/exenatide data was from a 24 week study to compare the safety and efficacy of the two medicines.

Slide 4, 'New Lyxumia provides significantly greater reductions in PPG excursion and exposure compared with liraglutide' featured a graph headed 'Lyxumia 20mcg once-daily significantly reduced PPG excursion vs liraglutide 1.8mg once daily (p<0.0001)'. In text less obvious than the headings, the x axis denoted the timing of the test medicine and of the test meal. Slide 28 was headed 'Comparative effects on glucagon supression' and the featured graph was headed 'Lyxumia 20mcg once-daily provides greater decrease in postmeal glucagon secretion than liraglutide 1.8mg once-daily'. There was no reference on slide 28 to a test meal. The Panel considered that it was not sufficiently clear that the data shown in both slides had been taken from a 28 day pharmacodynamic study and related only to the results from one standardised test meal and not to every meal of the day. The Panel noted the limitations of the study when considering long-term metabolic control. In the Panel's view, given the context in which they appeared ie a presentation designed to detail Lyxumia vs competitor medicines, the slides, although not required to include all of the data from Kapitza *et al*, did not give enough information about the study to enable readers to form their own opinion of the long-term therapeutic value of Lyxumia vs Victoza. In that regard the slides were misleading and a breach was ruled.

Novo Nordisk Limited complained about a Lyxumia (lixisenatide) presentation (ref GBIE.LYX.13.02.15) issued by Sanofi. Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicines and/or basal insulin when these, together with diet and exercise did not provide adequate glycaemic control. Novo Nordisk marketed Victoza (liraglutide which was also a GLP-1 receptor agonist for use in type 2 diabetes. Both medicines were administered once-daily.

Novo Nordisk referred to slides 4 and 23. Slide 4 was headed 'New Lyxumia provides significantly greater reductions in PPG [post-prandial glucose] excursion and exposure compared with liraglutide'. This was followed by a graph headed 'Lyxumia 20mcg once-daily significantly reduced PPG excursion vs liraglutide 1.8mg once daily (p<0.0001)' referenced to Kapitza *et al* (2013). The graph showed mean change from pre-meal plasma glucose. The test meal was given 30 minutes after the medicine and the graph showed the data for every 30 minutes for 4.5 hours.

Slide 23 was headed 'Comparative effects on glucagon suppression'. This was followed by a graph headed 'Lyxumia 20mcg once-daily provides a greater decrease in postmeal glucagon secretion than liraglutide 1.8mg once-daily' referenced to Kapitza *et al* and data on file. The graph compared mean plasma glucagon against theoretical time (0-4 hours 30 minutes). The final statement 'Glucagon AUC [area under curve] 0.30-4.30h (h-pg/mL) mean change from baseline. Estimated treatment difference – 21.2 p = 0.032' was referenced to data on file.

Kapitza *et al* assessed the pharmacodynamics of Lyxumia vs Victoza in type 2 diabetics insufficiently controlled on metformin.

COMPLAINT

Novo Nordisk alleged that the presentation was promotional and was aimed at health professionals who treated patients with type 2 diabetes. The presentation compared Lyxumia with other GLP-1 receptor agonists, Novo Nordisk's product Victoza and AstraZeneca and Bristol-Myers Squibb's product Bydureon (exenatide).

The efficacy sections (5.1) within the summaries of product characteristics (SPCs) for both products presented the data for glycaemic control first. The data, presented in tabular form, focussed on HbA_{1c} reductions, change in body weight and proportion of patients reaching the target of <7% HbA_{1c}. Novo Nordisk submitted that these three measures were the most recognised measures of diabetes/glycaemic control and were used extensively in clinical practice and well recognised and used by regulatory bodies. For example, The National Institute for Health and Care Excellence (NICE) in its clinical guideline for the management of type 2 diabetes in primary and secondary care stated that 'The risk of each of the microvascular and macrovascular complications of Type 2 diabetes and cataract extraction was strongly associated with hyperglycaemia as measured by updated mean HbA_{1c}'. The International Diabetes

Federation (IDF) recognised that 'There is currently a lack of direct randomised clinical trial evidence that correcting postmeal hyperglycaemia improves clinical outcomes [Level 1-]'. This was reflected and summarised in the most recent NICE clinical guideline 87 for the management of type 2 diabetes where criteria for the use and continuation of GLP-1 receptor agonists were linked to HbA_{1c} and weight lowering efficacy.

The SPC efficacy sections for both Lyxumia and Victoza also showed results for changes in fasting plasma glucose (FPG), postprandial glucose (PPG) and body weight. In addition effects on beta cell function, cardiovascular evaluation and paediatric population were discussed.

With regard to the comparison of Lyxumia and Victoza (slides 4 and 23), Novo Nordisk noted that Kapitza *et al* was a Sanofi sponsored study.

The data comparing Lyxumia and Victoza only presented reductions of PPG excursions after the test meal post-injection (slide 4) and the comparative effect on glucagon suppression (slide 23). Novo Nordisk alleged that presenting this primary endpoint in isolation to compare the two medicines was a biased, selective and unbalanced representation of Kapitza *et al*.

Novo Nordisk submitted that the correct way to present and compare efficacy looking at PPG excursions of once-daily GLP-1 receptor agonists was to present the 24 hour PPG profile. These data were published in Kapitza *et al* (figure 1B), however Sanofi had not presented these results. Slide 4 was entitled 'New Lyxumia provides significantly greater reductions in PPG excursion and exposure compared with liraglutide' which suggested that Lyxumia provided a greater reduction in PPG excursion than Victoza after every meal. Slide 4 failed to clarify that the claim was only true in respect of the test meal post-injection.

Kapitza *et al* had clearly shown that Victoza was superior (60% better) in the most clinically relevant measure of glucose control ie HbA_{1c} lowering efficacy. Sanofi did not provide these results in the presentation. This was surprising as Sanofi used HbA_{1c} efficacy data in slide 8 to show non-inferiority between Lyxumia and exenatide. This result was even more important considering Kapitza *et al* was the only head-to-head study which compared Victoza and Lyxumia. Novo Nordisk submitted that these results should thus not be ignored.

Another clinically relevant efficacy measure available from Kapitza *et al* was weight reduction. The study had shown that Victoza was superior to Lyxumia (50% better). Nevertheless, Sanofi did not present these results.

Sanofi also did not refer to the fasting plasma glucose (FPG) data in the comparison of Lyxumia and Victoza when Victoza provided significantly greater reductions in FPG than Lyxumia.

In summary, Novo Nordisk alleged that Sanofi had used data from Kapitza *et al* very selectively to present Lyxumia more favourably. Clinically relevant results showing advantages for Victoza (24 hour glucose control, HbA_{1c} reductions and weight reductions) had been ignored while only results of less clinically relevant outcome measures with advantages for Lyxumia (PPG reductions after the test meal only and glucagon suppression) had been presented. Novo Nordisk alleged that this was misleading in breach of Clause 7.2.

Novo Nordisk noted that Sanofi had stated in inter-company dialogue that it was not obliged to present any results representing efficacy, if such result related to secondary outcome measures. In Kapitza *et al* these were, *inter alia*, 24 hour glucose profile, HbA_{1c} reductions and weight lowering efficacy. In Novo Nordisk's view, Sanofi's argument was flawed as results of any study should be looked at in entirety; otherwise conclusions made on selective data were subject to bias. In addition, as discussed above, the results not shown by Sanofi were of upmost clinical relevance to the patient, physician and regulatory bodies.

In addition, FDA guidance stated 'the link between a modifying effect on postprandial glucose excursions to clinical outcomes is not sufficiently strong to consider the use of this pharmacodynamic endpoint as a surrogate for efficacy'. The same guidance stated 'For purposes of drug approval and labelling, final demonstration of efficacy should be based on reduction in HbA_{1c}, which will support an indication of glycaemic control', thereby emphasising the importance of HbA_{1c} reductions as an outcome measure.

To add to this, the European Medicines Agency (EMA) guideline on clinical investigation of medicines in the treatment or prevention of diabetes stated (when discussing insulin efficacy) that 'Reduction in the amplitude between postprandial hyperglycaemic peaks and fasting blood glucose values is desirable, but will not be accepted as a claim of superiority of a new insulin compared to an established insulin, unless accompanied by a relevant improvement in blood glucose control (measured by HbA_{1c}), hypoglycaemia or other clinically meaningful outcomes'. The EMA also noted that 'Weight gain is frequent in diabetic patients trying to implement intensive glucose control. The evolution of body weight will also be taken into account in the global evaluation of the efficacy and safety, particularly in type 2 diabetic patients'.

Based on the above, Novo Nordisk disagreed with Sanofi's view that HbA_{1c}/weight measurements and 24 hour glucose profiles were irrelevant and should not be presented based on the notion that they were secondary outcome measures in Kapitza *et al*.

Sanofi had also stated in inter-company dialogue that it was inappropriate to use 24 hour glucose profile data from Kapitza *et al* to substantiate any claims about efficacy of Victoza and Lyxumia beyond the test meal. Sanofi stated: 'It is clearly inappropriate therefore to make any claim about the postprandial effects outside of the test conditions - the scientific basis is clearly too weak to substantiate

this'. Novo Nordisk noted that the authors did not refer to this as being a scientific weakness of the study.

Kapitza *et al* stated 'At day 28, plasma glucose levels were much lower with [Lyxumia] than with [Victoza] during the post breakfast period (i.e., from ~45 minutes to ~4h after drug administration), whereas from 4.5h onwards (and before breakfast), plasma glucose levels were lower for [Victoza] than for [Lyxumia] at all-time points'. Furthermore the authors concluded, 'Specific patterns of coverage appeared to reflect the distinct pharmacokinetic profiles of [Lyxumia] and [Victoza], with [Lyxumia] providing particularly good coverage of breakfast-associated glycaemia, as clearly showed in the standardized breakfast meal test, and [Victoza] providing better fasting control and PPG coverage beyond the morning meal'. Therefore Sanofi's justification for not presenting these important findings was misplaced.

Sanofi had also used a similar argument to justify the absence of the HbA_{1c} efficacy results from Kapitza *et al* in the presentation. Kapitza *et al* demonstrated the mean HbA_{1c} decreased in both treatment groups from 7.2% to 6.9% (–0.32%) with Lyxumia vs. 7.4% to 6.9% (–0.51%) with Victoza, $p<0.01$. Sanofi stated that using the HbA_{1c} efficacy to compare Victoza and Lyxumia (as measured after 28 days) was scientifically weak and inappropriate. However, the only caution the authors expressed when discussing HbA_{1c} efficacy of both medicines, as correctly noted by Sanofi, was that 'direct conclusions with regard to long-term metabolic control should not be made'. This appeared to be a logical conclusion considering that full efficacy of any medicine in HbA_{1c} control would be shown after ~90 days due to the (patho) physiology of HbA_{1c}. Novo Nordisk noted that this comment did not preclude conclusions that could be made about comparative efficacy of both products after 28 days of exposure.

Nevertheless, it was well recognised that HbA_{1c} levels represent weighted average of glucose control over 90 days before measurement. Figure 2B in Tahara *et al*, (1995) showed the period of 30 days (similar to Kapitza *et al*) preceding the HbA_{1c} measurement consistently contributed to ~50% of final HbA_{1c} efficacy. This had been recognised by the National Glycohemoglobin Standardization Program (NGSP), 1996 responsible for harmonising HbA_{1c} testing. More recently this had been confirmed in the 'real world' setting and presented at 2013 European Association for the Study of Diabetes (EASD) conference. Hirst *et al*, (2013) showed that after just 4 weeks (as in Kapitza *et al*), HbA_{1c} reductions were ~60% of final HbA_{1c} reductions. The authors also suggested 'that many patients would benefit from returning to their GP earlier than 12 weeks following a change in their medication to have their HbA_{1c} checked'.

Therefore it was obvious that HbA_{1c} reductions after 4 weeks provided a good and consistent measure of glycaemic control showing ~50%-60% of final HbA_{1c} reductions, as shown by Hirst *et al* and Tahara *et al*. This was even more obvious when results of Kapitza *et al* were extrapolated using conclusions from Hirst *et al* and Tahara *et al*. Comparative HbA_{1c} reductions from Kapitza *et al* for Lyxumia and Victoza showed ~60% better lowering profile for Victoza. That was in line with the comparative placebo adjusted HbA_{1c} reductions detailed in the SPCs for both medicines (0.5% to 0.75% for Lyxumia and 0.90% to 1.1% for Victoza).

RESPONSE

Sanofi stated that the presentation at issue was delivered to health professionals by Lyxumia-trained representatives within a remote (internet based) sales call. The presentation was withdrawn from use on 25 June 2013 in keeping with the undertaking given in Case AUTH/2604/5/13. A new presentation was subsequently re-issued with amendments made to the elements relevant to that case, but slides 4 and 23 remained unchanged as they related to different information.

The complaint related to the use of data from Kapitza *et al*, a 28-day pharmacodynamic study which compared the effects of Lyxumia and Victoza on postprandial glucose excursion. The study demonstrated that there was a greater reduction in postprandial glucose excursion with Lyxumia than Victoza, as would be expected from the different pharmacokinetic profiles of each medicine (short- and long-acting agents respectively).

The study involved administration of study medicine to fasted subjects in the morning, followed by a standardised test meal (breakfast) 30 minutes later. The postprandial glucose excursion was assessed by eight blood glucose measurements in the four-hour period after the test meal, during which no further food intake occurred. After this tightly controlled period there was no standardisation of meals or meal times. Assessments were made at baseline (the day before the first administration of study medicine) and repeated on day 28 of treatment.

The primary outcome measure was the glucose excursion in the four-hour period after the standardised test meal, the primary endpoint was the change in post prandial glucose excursion from baseline to day 28. Secondary endpoints included the change in 24 hour glucose profile over the 24 hour study period (as measured by six blood glucose measurements between hours 6:30 and 24), and the change in HbA_{1c} from baseline to day 28.

Sanofi noted that Novo Nordisk had alleged that through presenting the primary endpoint of the study (the change in postprandial blood glucose concentration in the period 30 minutes to 4 hours 30 minutes after injection), but not every secondary endpoint studied (specifically change in HbA_{1c} from baseline, and the 24 blood glucose profile as opposed to the change 00:30 - 04:30hrs), Sanofi had misled the reader in breach of Clause 7.2.

Novo Nordisk had alleged that to fail to show the data beyond the four hour time period misled because Sanofi had not provided the reader with

information that suggested that Lyxumia was not effective for a full 24 hour period, and that this was required to demonstrate efficacy in the reduction of postprandial glucose excursion.

Sanofi disagreed with this position on the basis that the study design was focussed on the tightly controlled time period up until the 04:30 hour time point, and that to try to make any claims based on the data beyond this would in itself be misleading as the uncontrolled trial conditions did not allow conclusions to be drawn with the same level of rigour. As the primary endpoint was clearly presented without any attempt to mislead, Sanofi did not consider it appropriate to demonstrate those secondary endpoints where the design of the study had not permitted a robust confirmation of effect.

Sanofi noted that in Novo Nordisk's view, the correct way to demonstrate postprandial glucose excursion control was to show a 24 hour glucose profile, different to the 0:30 – 4:30 hour profile examined by the primary endpoint of this study.

Sanofi stated that, as a supportive trial rather than a pivotal study the endpoint demonstrated was not defined by regulatory requirements. Kapitza *et al* was designed to examine any difference in this specific pharmacodynamic effect between Lyxumia and Victoza, and thus understand the differences in mechanism of action, not to compare the efficacy of the two as defined by overall glycaemic control. The four hour window was selected because the post-meal glucose excursion would usually be completed in this period (as demonstrated in the results), hence to answer the scientific question 'What is the effect on postprandial glucose excursion?', a study of four hours was appropriate.

Although Sanofi understood Novo Nordisk's desire to see that conclusions were made on the data gathered beyond the primary outcome, it was clear that the study was designed with the strongest scientific focus on the four hour period in which the primary endpoint was assessed (ie the 0:30 – 4:30 hours time period). Beyond this time point the absence of controlled meals and meal times and the low frequency of blood testing did not allow such conclusions to be made with any certainty, and Sanofi submitted that this justified not using these secondary outcome measures in promotion.

With regard to the biological sampling, Sanofi explained that the blood testing schedule in the four hours related to the measure of the primary endpoint required the collection of eight samples at intervals of between 15 and 30 minutes. After this point there were only a further six samples taken, at intervals of between 2 and 9.5 hours. It was clear that this would weaken the ability to accurately measure the postprandial response after the initial control period and no meaningful conclusions could be made on the efficacy of either medicine in the period 4:30 – 24 hours.

Furthermore, the lack of standardisation of food intake and timing after 4:30 hours meant that there was no obvious time point that could be used to specifically compare the postprandial effects after mid-day and evening meals. This was clearly reflected in the results where the rise in blood glucose after the standardised breakfast meal was not repeated to the same magnitude at any point in the rest of the day at the baseline assessment – similarly sized excursions would normally be expected after mid-day and evening meals, and it was clear that these did not occur at baseline. Two graphs were provided to demonstrate what would be expected in response to normal mealtimes and what was observed by Kapitza *et al*. In the absence of a baseline post-prandial excursion, the scientific question of demonstrating a reduction could not be answered - it was inappropriate to draw any conclusion on the effects between Lyxumia and Victoza at these time points as the baseline observations did not document an increase in blood glucose that would be expected had a meal been taken.

Sanofi stated that one of the graphs from Polonsky *et al* (1998) demonstrated the postprandial excursions in patients with type 2 diabetes (upper line), showing a readily identifiable and similar magnitude excursion in relation to breakfast, mid-day and evening meals. In contrast, the second graph from Kapitza *et al* showed that the lack of controlled meals after the initial test meal resulted in no significant baseline postprandial excursion in response to any mid-day meal, and only a diminished excursion in response to an evening meal.

Sanofi therefore submitted that even if it were considered necessary to demonstrate postprandial effects over the course of a full day rather than in response to an individual test meal, it was not appropriate to use this study as the design did not allow conclusions to be drawn with certainty after the controlled period ended at 4 hours and 30 minutes. Sanofi noted that although Novo Nordisk proposed that Lyxumia did not have a postprandial effect for all three meals in the day when given once in the morning, this had been demonstrated conclusively by Lorenz *et al* (2013), and Sanofi used this study to illustrate this point in promotional material.

Lorenz *et al* demonstrated a reduction in post-prandial glucose excursion with Lyxumia after each of three meals in the day; each reduction was significant compared with the placebo-treated comparator group.

In conclusion, Sanofi strongly considered that to present data that was clearly not supported by the study design would be contrary to the Code – it would be unacceptable to make a claim about the effects of Lyxumia and Victoza from interpretation of the data outside of the controlled period of the study (ie beyond 4 hours and 30 minutes). Novo Nordisk's proposal to do this failed to recognise the letter and spirit nature of the Code.

Sanofi denied a breach of Clause 7.2.

Sanofi noted Novo Nordisk's allegation that it was misleading for Sanofi to fail to present the reduction in HbA_{1c} demonstrated as a secondary endpoint in Kapitza *et al*, as a relevant diabetes endpoint had

been missed out. In support of its position Novo Nordisk provided FDA and EMA guidelines, albeit those which defined the requirements for marketing authorization and not the promotion of medicines, that indicated that change in HbA_{1c} was the principle outcome that was required to demonstrate efficacy. Novo Nordisk argued that the fact that HbA_{1c} was an important endpoint was sufficient to require it to be presented in this material, even though it was a secondary, not primary, endpoint.

Sanofi contested that Kapitza *et al* was a short term pharmacodynamic study with the primary objective of examining the glycaemic response to Lyxumia and Victoza after a standard test breakfast. The data Sanofi presented was the primary endpoint and primary outcome of the study, and this could never be inappropriate.

Furthermore, Sanofi maintained that the presentation of secondary endpoints needed to be judged according to the scientific aims and objectives of the study. It was clear that the findings of a short-term pharmacodynamic study were not appropriate to support any conclusion on long-term glycaemic control, as stated by the authors. HbA_{1c} reflected the weighted average of blood glucose over the lifetime (90 - 120 days) of red-blood cells. HbA_{1c} was therefore recognised as only being able to provide an assessment of glucose control over the preceding 2-3 months, and was too coarse a measure to quantify effect in a 28 day study. Although Novo Nordisk quoted examples where HbA_{1c} might be measured in the short-term to indicate the direction of benefit (ie whether control was improving) rather than to quantify the degree of benefit in itself, Sanofi noted that the 0.3% - 0.5% reductions in HbA_{1c} demonstrated by Kapitza *et al* were significantly lower than the reductions quoted in the Lyxumia and Victoza SPCs, which fell broadly in the range of 0.75% - 2.0%; this further suggested that these results should not be used to compare metabolic control.

Regardless, the FDA and EMA notes for guidance concerned the requirements for demonstration of efficacy in appropriately designed confirmatory trials of a minimum 6-12 months – whereas Kapitza *et al* lasted just 28 days and was mechanistic pharmacodynamic study, not a confirmatory efficacy study. With regard to studies of 8 weeks duration or less, the guidance notes also stated that plasma glucose was the appropriate outcome measure, as reported by Kapitza *et al* (EMA Guidance section 4.1.3.2). The use of these guidelines to suggest that HbA_{1c} was the most important measure of glycaemic control was therefore entirely inappropriate, and should certainly not be used to suggest how the results of Kapitza *et al* should be presented in promotional material.

In summary, Sanofi reiterated that Kapitza *et al* was a 4 week study and it was therefore entirely inappropriate to draw any conclusions on long-term glycaemic control. To make any claim regarding superiority of change in HbA_{1c} would similarly be completely at odds with the intent of the authors who stated, 'With respect to clinical reality, a limitation of this study is the relatively short observation time of 28 days. Indeed, direct conclusions with regard to long-term metabolic control should not be made.'

Sanofi therefore submitted that omission of this information rather than its inclusion was the appropriate course of action, required by the Code to avoid misleading the reader through presentation of an inappropriate comparison.

With regard to Novo Nordisk's view that changes in weight should be presented, Sanofi submitted that the same reasoning applied – Kapitza *et al* was of too short a duration to draw any conclusion on weight loss. The authors' recognition that a 28 day duration was of too short a time to make any conclusion on metabolic outcomes applied as equally to weight as it did to HbA_{1c}, and to show this would have exactly the same level of disrespect for the requirements of the Code as it would to show the change in HbA_{1c}.

In summary, Sanofi submitted that it was inappropriate to draw conclusions on the outcomes of metabolic parameters such as HbA_{1c} and weight due to the short-term nature of Kapitza *et al*, and that to present this information would be akin to making claims incapable of substantiation, itself breaches Clauses 7.2 and 7.3.

With regard to fasting plasma glucose, Sanofi noted that Novo Nordisk had not previously raised this issue within inter-company dialogue, and it was therefore surprised to see it raised within this complaint.

In response Sanofi questioned the relevance of a reduction in fasting glucose levels in a study that examined the postprandial response. Although a statistically different result had been demonstrated, it was in a secondary endpoint that was not directly relevant to the primary objective of the study. The fact that the result existed in itself was not sufficient reason to see it included in promotional material, and given that the outcome was disconnected to the primary objective of the study there was little logical rationale to include it in material, and nor was it a requirement of the Code. No breach had previously been suggested through its omission, nor did Sanofi consider that one had occurred through its omission.

In conclusion, Sanofi submitted that the allegations were inappropriate – Kapitza *et al* clearly indicated that the study was of too short a duration to draw conclusions on metabolic control, and the guidelines for development quoted by Novo Nordisk similarly supported this position. To be alleged to be in breach through omitting to follow both these directions was therefore poorly considered, and Sanofi was confident that high standards had been maintained and that no breach of the Code had occurred.

In response to a request for further information, Sanofi provided a copy of an additional reference and a copy of the updated presentation (ref GBIE. LYX.13.06.11(3)).

PANEL RULING

The Panel noted that the presentation referred to by Novo Nordisk was entitled 'When it is time to add to basal insulin' followed by a reference to Lyxumia and 'A positive addition can make all the difference'. The next two slides were headed 'Choices to control PPG can be complex for patients on basal insulin' and 'Prandial GLP-1 receptor agonists have a greater effect on PPG than non-prandial agents'. The Panel noted that the presentation had been withdrawn following Case AUTH/2604/5/13. Sanofi stated that slides 4 and 23 remained unchanged and were still in use. The Panel noted that in the updated presentation entitled 'A positive addition when it's time to add to basal insulin', slide 23 had been amended such that the x axis recorded data from 1 hour after study drug administration (slide 23 had originally shown data points for 0 hours and 30 minutes and the x axis was labelled 'Theoretical time').

The Panel noted that the presentation referred to by Novo Nordisk (ref GBIE.LYX.13.02.15) was used by representatives in a remote (internet-based) sales call with health professionals. In the Panel's view, the presentation was designed, at least in part, to compare the clinical use of the available GLP-1 receptor agonists and the treatment choices available in that regard for type 2 diabetics uncontrolled on existing treatment regimens. However, as Victoza was only licensed to be given in combination with oral antidiabetic medicines and not insulin, the Panel queried whether a comparison of Lyxumia with Victoza should have been included at all in a presentation entitled 'When it's time to add to basal insulin'. The comparative information about Lyxumia and Victoza was limited to PPG excursion (slide 4) and post-meal glucagon secretion (slide 23) data from Kapitza *et al* which was a pharmacodynamic comparison, and according to Novo Nordisk, the only direct comparison, of the two medicines.

The Panel noted Sanofi's submission that Kapitza *et al* was not a comparison of the efficacy of the two medicines as defined by overall glycaemic control. The primary efficacy endpoint was the change in baseline to day 28 in the area under the plasma-glucose concentration time curve in the 4 hour period after the start of a standardised breakfast test meal. Secondary efficacy measures included mean HbA_{1c} and 24 hour glucose control. The Panel noted Sanofi's submission that the duration of the study (28 days) and the fact that mean HbA_{1c} was a secondary outcome in a study which was designed to measure short-term pharmacodynamic differences between Lyxumia and Victoza, meant that any differences noted between the two in terms of glycaemic control might not reflect clinical use. The authors themselves had stated in the discussion section of the paper that 'With respect to clinical reality, a limitation of this study is the relatively short observation time of 28 days. Indeed direct conclusions with regard to long-term metabolic control should not be made'. The Panel noted Novo Nordisk's submission that although Sanofi had not shown the HbA_{1c} efficacy data for Lyxumia vs Victoza (based on Kapitza *et al*), the company had included such data for Lyxumia vs exenatide. The Panel noted, however, that the Lyxumia/exenatide data was longer term data taken from Rosenstock *et al* (2013), a 24 week study to compare the safety and efficacy of the two medicines.

The Panel noted that slide 4 was headed 'New Lyxumia provides significantly greater reductions in PPG excursion and exposure compared with liraglutide'. The featured graph was headed 'Lyxumia 20mcg once-daily significantly reduced PPG excursion vs liraglutide 1.8mg once daily ($p<0.0001$)'. In text less obvious than the headings, the x axis denoted the timing of the test medicine and of the test meal. Slide 28 was headed 'Comparative effects on glucagon supression' and the featured graph was headed 'Lyxumia 20mcg once-daily provides greater decrease in postmeal glucagon secretion than liraglutide 1.8mg once-daily'. There was no reference on slide 28 to a test meal. The Panel considered that it was not sufficiently clear that the data shown in both slides had been taken from a 28 day pharmacodynamic study and related only to the results from one standardised test meal and not to every meal of the day. The Panel noted the authors' comments cited above with regard to the limitations of the study when considering long-term metabolic control. In the Panel's view, given the context in which they appeared ie a presentation designed to detail Lyxumia vs competitor medicines, the slides, although not required to include all of the data from Kapitza *et al*, did not give enough information about the study to enable readers to form their own opinion of the long-term therapeutic value of Lyxumia vs Victoza. In that regard the slides were misleading and a breach of Clause 7.2 was ruled.

Complaint received **14 November 2013**

Case completed **30 January 2014**

ADVERTISING AGENCY EMPLOYEE v BAYER

Advertisements on media website

An advertising agency employee alleged a breach of the Code in that advertisements for Sativex (delta-9-tetrahydrocannabinol and cannabidiol) in the treatment of spasticity associated with multiple sclerosis had been posted on a creative media website which was not password protected; anyone could access the website.

The detailed response from Bayer is given below.

The Panel noted that as a result of an advertising agency submitting the Sativex campaign for an award, and being shortlisted, the advertisements at issue had appeared on the creative media website. The website was a US-based, professional website; it was not directed at the general public. In that regard, the Panel noted that the complainant worked in an advertising agency. Data showed that 83% of those visiting the website were media professionals working in marketing (12%), design (19%) or advertising (52%).

The Panel noted that the advertisements for Sativex, a prescription only medicine, had been placed on the US website, albeit indirectly, by the advertising agency engaged by Bayer; the advertisements referred to the UK cost of the medicine and thus, indirectly, to the use of Sativex in the UK. The Panel thus considered that the matter came within the scope of the Code.

The Panel acknowledged that creative agencies would want to enter their work for awards and that as a result, examples of such work might appear, *inter alia*, on open access websites. The Panel considered it would be prudent if the potential for such submissions was addressed in the contract between the pharmaceutical company and its agency at the outset. The website in this case was directed specifically at creative media professionals and although anyone could access it, it was not aimed at the general public. The Panel noted the website's readership demographics and considered that in the particular circumstances of this case, Sativex had not been promoted to the public. No breach of the Code was ruled. High standards had been maintained. No breach of the Code was ruled including no breach of Clause 2.

An advertising agency employee provided a screenshot from a creative media website which featured advertisements for Sativex (delta-9-tetrahydrocannabinol and cannabidiol) in the treatment of spasticity associated with multiple sclerosis.

COMPLAINT

The complainant alleged a breach of the Code in that the website was not password protected and anyone in any country could access it.

When writing to Bayer, the Authority asked it to respond in relation to Clauses 2, 9.1 and 22.1 of the Code.

RESPONSE

Bayer submitted that reproductions of advertisements for prescription only medicines (POMs) were widespread in the pharmaceutical advertising media; they appeared in printed materials, related online sites and related professional accounts on social media without any restrictions on access by the public. Bayer did not know of any previous Code breaches which related to the display of POM advertising within such professional media. Bayer noted that in Case AUTH/2576/2/13 the Panel made clear its position that creative agencies and individuals might reasonably be expected to show examples of their work in an appropriate professional context.

In the complaint now at issue the complainant appeared to have downloaded Sativex advertisements from the US-based media website.

Three Sativex advertisements for health professionals appeared on the website because the Sativex UK campaign won an international award. Bayer submitted that there was no precedent for the Code being used to prevent creative healthcare advertising agencies, much of whose business was generated by advertising POMs, from entering such work for awards, nor from showing examples of their work in legitimate professional media, whether in the UK or, as in this case, elsewhere.

Bayer stated that the advertising agency which worked on Sativex in the UK, had undertaken a comprehensive internal investigation into this complaint and reported in full to Bayer. Bayer was satisfied that the agency's actions had complied with the Code and that it had made every effort to ensure all its personnel were fully trained on the Code.

Bayer noted that the agency had entered the most recent UK Sativex campaign to a long-established, US-based, international awards competition for advertising, design, interactive and communications. The agency was emailed on 11 November 2013 that the Sativex entries had been shortlisted. The email stated that there would not be an awards ceremony

this year but that all winning work would appear on a creative media website and two other reputable US-based professional creative media sites. It was announced on these sites on 19 November that Sativex had won a healthcare award, the agency became aware of the award on 20 November, the day that this complaint was submitted.

The creative media website was a global advertising archive and community run by a US media company, whose mission statement positioned it as 'the leading provider of jobs, news, education, events, and research for the media industry. Our mission is to help media professionals succeed and grow in their careers as we provide them with opportunities to acquire new positions, knowledge, skills, and connections'. The audience for the site was composed almost exclusively of creative media professionals, >90% of users identified themselves as such. Bayer noted that the complainant worked for an advertising agency and thus also fell within this professional category.

The creative media website made it clear that it was intended as a resource for creative professionals, encouraging critical comment on a wide range of advertisements, with an emphasis on sharing best advertising practice and recognising high creative standards.

Bayer submitted that the creative media website at issue and its linked Twitter feed were therefore well-established US creative professional sites, owned by a bona fide US media company, with a global audience of media professionals. These sites were not directed at the UK general public. They sought only to present and discuss the creative merits of the advertisement itself, not the merits of any product being advertised. There was clearly no intention to encourage any patient to request a prescription of Sativex from a UK doctor and, given the content and US base of the website, it seemed highly improbable that any UK patient would seek it out.

Bayer submitted that it considered that the site fell outwith the Code and that the advertising agency's submission of the Sativex campaign for the healthcare awards was consistent with reasonable business interests as endorsed by the Panel in Case AUTH/2576/2/13, in showing examples of its work in an appropriate professional context. There was no advertisement of Sativex directed towards the UK public and thus there was no breach of Clause 22.1.

Bayer noted that all of the agency's employees involved in creating work for pharmaceutical companies had to have a good understanding of the Code and other relevant advertising codes and standards. The agency trained all relevant new employees on the Code as part of their induction and held regular refresher and update training. Details were provided.

Further the current contract between Bayer and its agency for the purposes of Sativex marketing, stated, *inter alia*, that the agency should abide by the Code and ensure that all advertising placed by the agency was legal, decent, honest and truthful.

Thus Bayer and its agency placed the highest value on adherence to the Code and this was reflected in the contractual arrangements between them. Additionally, Bayer could demonstrate that all personnel involved in both companies had been fully trained on the requirements of the Code. The company thus denied any breach of Clauses 2 or 9.1 of the Code.

Taking all the above into consideration, Bayer submitted that it had not breached the Code. The complaint did not fall within the scope of the Code and Bayer and its agency had maintained the highest professional and Code-compliance standards at all times.

PANEL RULING

The Panel noted that as a result of the advertising agency submitting the Sativex campaign for an award, and being shortlisted, the advertisements at issue had appeared on the creative media website. The website was a US-based, professional website for the creative media; it was not directed at the general public. In that regard, the Panel noted that the complainant worked in an advertising agency. Data from the creative media website showed that 83% of those visiting its website were media professionals working in marketing (12%), design (19%) or advertising (52%). Eight percent were software developers and IT and 'others' accounted for the remaining 9%.

The Panel disagreed with Bayer's submission that the matter was not within the scope of the Code. The Panel noted that Clause 24.2 stated that information or promotional material about a prescription only medicine which was placed on the Internet outside the UK would be regarded as coming within the scope of the Code if it was placed there by a UK company or an affiliate of a UK company or at the instigation or with the authority of such a company and it made specific reference to the availability or use of the medicine in the UK. In that regard, the Panel noted that the advertisements for Sativex, a prescription only medicine, had been placed on the US website, albeit indirectly, by the advertising agency engaged by Bayer; the advertisements referred to the UK cost of the medicine and thus, indirectly, to the use of Sativex in the UK. The Panel thus considered that the conditions set out in Clause 24.2 had been met and so the Code applied.

The Panel acknowledged that creative agencies would want to enter their work for awards and that as a result, examples of such work might appear, *inter alia*, on open access websites. The Panel considered it would be prudent if the potential for such submissions was addressed in the contract between the pharmaceutical company and its agency at the outset. The website in this case was directed specifically at the creative media and

although anyone could access it, it was not aimed at the general public. The Panel noted the website's readership demographics and considered that in the particular circumstances of this case, Sativex had not been promoted to the public. No breach of Clause 22.1 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

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

Complaint received **20 November 2013**

Case completed **9 January 2014**

ADVERTISING AGENCY EMPLOYEE v LILLY

Advertisements on media website

An advertising agency employee alleged a breach of the Code in that an advertisement about maintenance treatment in advanced lung cancer had been posted on a creative media website which was not password protected; anyone in any country could access it. The Eli Lilly & Company logo was in the bottom right hand corner of the advertisement.

The detailed response from Lilly is given below.

The Panel noted that the advertisement at issue featured a photograph of an older woman who appeared to be helping a young girl to knit. Next to the lady's seat was a parking meter. Below the photograph was the question 'Why put a time limit on advanced lung cancer treatment?' Subsequent text explained that although traditionally, patients with advanced non-small cell lung cancer (NSCLC) were limited to a fixed number of first-line treatment cycles, new evidence showed that maintenance therapy controlled tumour growth and allowed people to maintain quality of life for longer. Readers were referred to a website which linked directly to the Lilly oncology website. From the homepage of that website, health professionals were directed to a page from where they were invited to download a slidekit on maintenance therapy in advanced NSCLC. The slidekit included the UK prescribing information for Alimta (pemetrexed) which was licensed, *inter alia*, for use in advanced NSCLC. In the Panel's view, the slidekit promoted Alimta. The homepage of the website directed patients to a page about Lilly oncology which provided corporate information about the company and also information about relevant patient websites.

The Panel noted Lilly's submission that, without its agreement and contrary to the terms of its contract, the advertising agency had submitted the advertisement for an award. The advertisement was subsequently selected as a finalist and thus appeared on the creative media website. The Panel noted Lilly's submission that the creative media website was an online advertising archive and community based in the US and intended for a specialised audience of media professionals.

The Panel noted that the advertisement had been placed on the US website, albeit indirectly, by the advertising agency engaged by Lilly; the advertisement referred health professionals to a website from which they could download a promotional slidekit for Alimta which included the UK prescribing information for the medicine. The Panel thus considered that the matter came within the scope of the Code.

The Panel acknowledged that creative agencies would want to enter their work for awards and that as a result, examples of such work might appear, *inter alia*, on open access websites. The website in this case was directed specifically at the creative media and although anyone could access it, it was not aimed at the general public. In addition the website linked to the advertisement at issue provided information for health professionals and for the public; the two sections were clearly separated and the intended audiences identified. The Panel noted the creative media website's readership demographics and considered that in the particular circumstances of this case, Alimta had not been promoted to the public. No breach of the Code was ruled. High standards had been maintained and no breach of the Code was ruled including no breach of Clause 2.

An advertising agency employee provided a screenshot from a creative media website which featured an advertisement about maintenance treatment in advanced lung cancer. The advertisement featured the photograph of an older lady sitting in a chair apparently helping a child to knit. The Eli Lilly & Company logo was in the bottom right hand corner.

COMPLAINT

The complainant alleged a breach of the Code in that the website was not password protected and anyone in any country could access it.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 9.1 and 22.1 of the Code.

RESPONSE

Lilly submitted that the advertisement was developed as part of the company's campaign on maintenance therapy in non-small cell lung cancer (NSCLC). The campaign was intended to increase health professionals' awareness of the concept of maintenance treatment in NSCLC, which was an emerging treatment option when the advertisement was developed. It was a therapeutic approach by which one of the chemotherapy medicines given first-line or a new medicine was continued until progression of the disease. Randomized controlled trials had demonstrated that maintenance treatment could delay the progress of lung cancer and was now recommended in several treatment guidelines in oncology. Maintenance was intended to help patients with the symptoms of cancer, and, hopefully improve survival time.

The campaign was developed by Lilly for use between January 2013 and the end of January 2014. It had been distributed through a variety of communication channels.

The focus of the campaign and of the advertisement was not a medicine, but the concept of maintenance therapy for NSCLC as highlighted above. A number of approved treatment options in the maintenance setting were available for NSCLC from different manufacturers and no Lilly product was mentioned on the advertisement. It thus could not be claimed that Lilly had advertised any Lilly medicine to the public either directly or by implication. Lilly firmly believe that there was no prescription only medicine advertising visible to the public as alleged by the complainant or at all. Lilly denied a breach of Clause 22.1.

Lilly also denied that the display of the advertisement on the creative media website was in breach of Clause 9.1. The imagery used on the advertisement was of absolute good taste and appropriate for the target audience and also to be used in the public domain. Further, as highlighted above no prescription only medicine was promoted. Therefore, the use of a child could not imply that a treatment was licensed for children (no treatment was advertised). Lilly submitted that the advertisement was certified in compliance with Clause 14.

Lilly did not consider that it had breached Clauses 22.1 or 9.1 and as a consequence, it did not consider that the publication of the advertisement on the creative media website was such as to be likely to bring discredit upon, or reduce confidence in, the pharmaceutical industry.

In response to a request for further information, Lilly stated that the campaign was developed by an advertising agency engaged only to create the contents of the campaign, ie to develop the advertisements which formed part of it. It was not contracted by Lilly in order to place the advertisement on any media channels.

Lilly further noted that the terms and conditions of its contract with the agency included a confidentiality clause which required the agency to retain confidential information in strict confidence and not use it for its own benefit without Lilly's prior written agreement. Furthermore, the terms and conditions stated that 'Each party shall ensure that it and its activities under this Contract shall at all times comply with all applicable laws, regulations and industry codes [...]'.

Lilly submitted that it did not pay the advertising agency to publish the advertisement or other materials on the creative media website or on any other media channels, or otherwise authorise it to do so. The advertising agency caused the advertisement to be published on the creative media website on its own initiative.

The advertisement was submitted by the advertising agency, in the absence of any inputs or permission from Lilly and in breach of the above mentioned confidentiality obligation, for a healthcare award, an internet-based competition for creative works in the healthcare arena. The agency had advised Lilly that the winning works of the 2013 award were meant to be published on a creative media website and another media website, from Monday, 18 November; and the advertisement was a finalist, not a winner, of the awards, and consequently it should not have been published on any of the above websites. However, the webmaster of the creative media website uploaded all of the 2013 healthcare awards finalist works onto the website on the same day in which the complaint was filed. This included the advertisement in question.

Lilly stated that it was unaware of all of the above.

The creative media website was an online advertising archive and community located in the US and owned by a media company. The creative media website was intended for a specialised audience of media professionals.

With regard to certification of the advertisement, as a conservative approach, Lilly considered that the advertisement needed certification. Although it did not promote any Lilly medicine, the advertisement was intended to raise health professionals' awareness of maintenance treatment in NSCLC. However, there was a statement on the certification which clarified this ie 'This concept is designed to promote the rational for the use of maintenance therapy in the treatment of advanced NSCLC. This material will not be used to promote ALIMTA [...]' (Alimta was a Lilly medicine for treatment of NSCLC). Lilly considered that this statement clarified the non-promotional nature of the item.

PANEL RULING

The Panel noted that the advertisement at issue featured a photograph of a seated older woman who appeared to be helping a young girl to knit. Next to the lady's seat was a parking meter. Below the photograph was the question 'Why put a time limit on advanced lung cancer treatment?' Subsequent text explained that although traditionally, patients with advanced NSCLC were limited to a fixed number of first-line treatment cycles, new evidence showed that maintenance therapy controlled tumour growth and allowed people to maintain quality of life for longer. Readers were referred to a website which linked directly to the Lilly oncology website. From the homepage of that website, health professionals were directed to a page about maintenance therapy for advanced lung cancer and invited to download an educational slidekit on maintenance therapy in advanced NSCLC. The slidekit included the UK prescribing information for Alimta (pemetrexed) which was licensed, *inter alia*, for use in advanced NSCLC. In that regard, the Panel disagreed with Lilly's submission that the campaign did not focus on a medicine. In the Panel's view, the slidekit promoted Alimta. The homepage of the website directed patients to a page about Lilly oncology which provided corporate information about the company and also information about relevant patient websites.

The Panel noted Lilly's submission that, without the company's agreement and contrary to the terms of its contract, the advertising agency had submitted

the advertisement for an award. The advertisement was subsequently selected as a finalist and thus appeared on the creative media website. The Panel noted Lilly's submission that the creative media website was an online advertising archive and community based in the US and intended for a specialised audience of media professionals.

The Panel noted that Clause 24.2 stated that information or promotional material about a prescription only medicine which was placed on the internet outside the UK would be regarded as coming within the scope of the Code if it was placed there by a UK company or an affiliate of a UK company or at the instigation or with the authority of such a company and it made specific reference to the availability or use of the medicine in the UK. In that regard, the Panel noted that the advertisement had been placed on the US website, albeit indirectly, by the advertising agency engaged by Lilly; the advertisement referred health professionals to a website from which they could download a promotional slidekit for Alimta. The slidekit included the UK prescribing information for the medicine. The Panel thus considered that the conditions set out in Clause 24.2 had been met and so the Code applied.

The Panel acknowledged that creative agencies would want to enter their work for awards and that as a result, examples of such work might appear, *inter alia*, on open access websites. The website in this case was directed specifically at the creative media and although anyone could access it, it was not aimed at the general public. In addition the website linked to the advertisement at issue provided information for health professionals and for the public; the two sections were clearly separated and the intended audiences identified. The Panel noted the creative media website's readership demographics and considered that in the particular circumstances of this case, Alimta had not been promoted to the public. No breach of Clause 22.1 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

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

Complaint received **20 November 2013**

Case completed **24 January 2014**

HOSPITAL DOCTOR v GLAXOSMITHKLINE

Invitation to exhibition stand

A hospital doctor complained about the strapline 'do more, feel better, live longer' on an invitation to visit GlaxoSmithKline's stands at the winter 2013 meeting of the British Thoracic Society (BTS). Whilst the complainant was sure that 'do more, feel better, live longer' was an appropriate aspiration for GlaxoSmithKline, he noted that none of the company's respiratory products made you live longer.

Whilst the complainant understood that this was an innocent combination of company logo with respiratory invitation, he thought it might be misinterpreted; in particular it inferred that GlaxoSmithKline's lead product Seretide [salmeterol/fluticasone propionate] could make you live longer when in fact the TORCH [Towards a Revolution in COPD Health] study showed that there was no such effect.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that the flyer/invitation sent to the complainant was titled 'GSK Respiratory' and contained the GlaxoSmithKline logo with the strapline 'do more, feel better, live longer' in the top-right hand corner. Below the title was the phrase *'Working to eradicate the patient impact of COPD & asthma'* followed by 'Taking a *patient-centred* approach to deliver *a range of medicines to enable clinicians* to tailor treatment to patients' needs'. Beneath this was a text box that included, *inter alia*, an invitation to 'Come and talk to us on our exhibition stands: ….'. Stand numbers and details of their location were provided as well as contact details for further information.

The Panel noted GlaxoSmithKline's submission that the purpose of the flyer was to highlight its support and corporate presence at the meeting. The flyer clearly encouraged visiting the company's exhibition stands including the promotional stands.

The Panel noted GlaxoSmithKline's submission that in previous cases the Panel had accepted that, in the absence of a specific product claim, a corporate mission statement in a therapy area was non-promotional and that a corporate logo and strapline were independent from a product claim when there was sufficient separation between the two. The Panel considered that there were significant differences between those cases and that presently at issue. The Panel noted that each case was judged on its own merits.

Turning to this case, the Panel considered that in certain circumstances a corporate mission statement might be regarded as promotional: its content and context were relevant. The Panel noted GlaxoSmithKline's submission that the flyer did not refer specifically to any product and that branding was corporate rather than product-specific. However, the Panel noted that the flyer was an invitation to visit, *inter alia*, GlaxoSmithKline's promotional stands and that it mentioned COPD and asthma.

The Panel noted GlaxoSmithKline's full corporate mission statement: 'to improve the quality of human life by helping people to do more, feel better and live longer'. The Panel considered that the abridged statement 'do more, feel better, live longer' as it appeared on the flyer in question was different. Context was also important.

The abridged mission statement appeared on a flyer which referred to GlaxoSmithKline respiratory and the patient impact of COPD and asthma and invited attendance at, *inter alia*, three promotional stands. Whilst the Panel accepted that 'do more' might be considered a statement of general corporate intent, 'feel better, live longer', within the context of an item headed GlaxoSmithKline respiratory and which referred to eradication of the patient impact of COPD and asthma, could refer to the effect of GlaxoSmithKline's respiratory product portfolio. Indeed this was the view of the complainant. In this regard the Panel noted that whilst the statement was physically separate from the main body of text, visually it had the same colour font and font style as the rest of the item and appeared to be an integral part of the whole. The Panel thus considered on balance, within the context of this particular item, that the statement was a claim for GlaxoSmithKline's respiratory portfolio, including Seretide.

The Panel noted that the complainant had the burden of proving his complaint on the balance of probabilities. The Panel noted the complainant's allegation that the claim 'do more, feel better, live longer' implied, *inter alia*, that Seretide could make you live longer. According to the complainant the TORCH study did not support this. The Panel considered that the claim was thus misleading in relation to Seretide and a breach of the Code was ruled.

Upon appeal from GlaxoSmithKline the Appeal Board acknowledged that in certain circumstances a corporate statement might be regarded as promotional.

The Appeal Board noted that the bright orange invitation was entitled 'GSK Respiratory' and in the top right-hand corner next to the GlaxoSmithKline corporate logo was the strapline 'do more, feel better, live longer'. The Appeal Board considered the positioning of the strapline to the right of the logo, and therefore on the outer right edge of the invitation, separated it from the body of the

invitation. The invitation/flyer invited readers to visit the company's promotional and medical exhibition stands. In that regard the Appeal Board noted GlaxoSmithKline's submission that its promotional stands at the meeting promoted Relvar Ellipta and not Seretide.

The Appeal Board further noted that within GlaxoSmithKline orange was reserved for corporate branding; it was not linked to a promoted product. The Appeal Board noted that the invitation did not mention any specific medicines. The Appeal Board considered that the strapline 'do more, feel better, live longer' as it appeared in the top right-hand corner of the invitation/flyer in question did not relate to, or make any claims for, any particular medicine, including Seretide. The Appeal Board ruled no breach of the Code. The appeal was successful.

The Panel noted its finding above that the phrase 'do more, feel better, live longer' was a claim for GlaxoSmithKline's respiratory portfolio. However the complainant had not submitted any material or evidence to support his position in relation to the rest of the medicines in GlaxoSmithKline's respiratory portfolio. The Panel noted that the complainant bore the burden of proof and considered that he had not established his case on the balance of probabilities. Whilst the Panel was concerned about the phrase in question, in the absence of any evidence on this point and on this narrow ground alone the Panel did not consider the claim misleading or all embracing in relation to the rest of GlaxoSmithKline's respiratory portfolio. No breach of the Code was ruled.

A hospital doctor complained about an invitation (ref UK/COM/0199/13) which he had received from GlaxoSmithKline UK Limited to visit the company's stands at the winter meeting of the British Thoracic Society (BTS). The invitation stated 'Working to eradicate the patient impact of COPD [chronic obstructive pulmonary disease] & asthma', 'Taking a patient-centred approach to deliver a range of medicines to enable clinicians to tailor treatment to patients' needs'. No specific medicines were named. The recipient was then invited to visit the company stands details of which were provided.

COMPLAINT

The complainant noted that in the top right-hand corner of the invitation was the GlaxoSmithKline logo with the strapline 'do more, feel better, live longer'. Whilst the complainant was sure this was an appropriate aspiration for GlaxoSmithKline, the conjunction of these two statements on the same invitation was factually incorrect. None of the GlaxoSmithKline respiratory products made you live longer.

Whilst the complainant understood that this was an innocent combination of company logo with respiratory invitation, he thought it might be misinterpreted; in particular it inferred that GlaxoSmithKline's lead product Seretide [salmeterol/fluticasone propionate] could make you live longer when in fact the TORCH [Towards a Revolution in COPD Health] study showed that there was no such effect.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 7.2 and 7.10 of the Code.

RESPONSE

GlaxoSmithKline stated that the invitation in question was sent as a flyer to Thorax journal subscribers with its December 2013 issue (Volume 68; Issue 12). A copy of the final version along with its approval certificate was provided. The purpose of this flyer was to highlight GlaxoSmithKline's support and corporate presence at the winter 2013 Meeting of the British Thoracic Society. The flyer did not refer specifically to any GlaxoSmithKline product and therefore was specifically created with its corporate branding rather than a product-specific branding.

The flyer contained GlaxoSmithKline's corporate logo and strapline that included GlaxoSmithKline's corporate mission: to improve the quality of human life by helping people to do more, feel better and live longer. GlaxoSmithKline believed that it was sufficiently clear that the logo and associated corporate mission did not imply any benefit or claim about a particular product. In support of this, the positioning of the corporate logo and strapline (in the top right hand corner) was sufficiently separated from the main body of the text, further distinguishing this as a corporate mission. Since this mission strapline did not relate to any specific product and no product was referred to in the flyer, GlaxoSmithKline had not provided any prescribing information or summary of product characteristics (SPC).

Following the introduction of the new corporate logo, GlaxoSmithKline UK issued internal guidance to ensure its appropriate use and prevent any misunderstanding; this pre-dated the complaint. This guidance stated that the corporate mission strapline was not to be used on any communications or materials, including emails, detail aids, meeting slides etc, which contained information about a GlaxoSmithKline product that were used with external parties. This was issued to ensure that the corporate mission strapline was not misconstrued as a product-specific claim. The guidance on use with emails was subsequently clarified to exclude 1:1 correspondence emails as the sign off was positioned in such a way that it should not be misconstrued as a claim; an example of such sign-off was provided.

The exhibition stands referred to on the invitation would promote Relvar Ellipta (fluticasone furoate/vilanterol), which had blue and grey branding. These promotional stands contained corporate logos without the corporate mission statement in accordance with the GlaxoSmithKline internal guidance referred to above.

GlaxoSmithKline noted that a second flyer was placed in delegates' bags to raise awareness of its support for the meeting. Both flyers contained

GlaxoSmithKline's respiratory vision but the flyer for the delegate bag also referred to GlaxoSmithKline's stands. However, the two flyers were mixed up by the printers and this was why the certificate for the flyer in question had the wrong intended use. Investigation had revealed that the mailing house had delivered the wrong item to the journal publisher. The email correspondence confirming GlaxoSmithKline's original instructions to the printer relating to these items and an email confirming the error on the part of their provider were provided. GlaxoSmithKline was working with its suppliers to take the required action to prevent any similar episodes happening in the future.

A gallery note had now been added to the job bag of the flyer that was distributed in error in Thorax in order to document the error and to confirm that the content was still appropriate for use in Thorax. In addition, the flyer intended for Thorax would now be placed in the delegate's bag and had been recertified for such use.

GlaxoSmithKline noted that the Panel had previously accepted a corporate mission statement in a therapy area to be non-promotional in the absence of a specific product claim (Case AUTH/1920/11/06). The Panel had also previously accepted a corporate logo and strapline to be independent from a product claim when there was sufficient separation between the two (Case AUTH/2216/3/09).

GlaxoSmithKline was confident that in the absence of any product-specific claim and due to its clear separation from the main body of the text, GlaxoSmithKline's corporate logo and strapline on this flyer could clearly be identified as such and should not be considered a claim about a GlaxoSmithKline product. The flyer was also produced in line with corporate branding rather than product specific branding. Therefore, GlaxoSmithKline believed this flyer fell outside the scope of Clauses 7.2 or 7.10.

PANEL RULING

The Panel noted that the flyer/invitation sent to the complainant was titled 'GSK Respiratory' and contained the GlaxoSmithKline logo with the strapline 'do more, feel better, live longer' in the top right-hand corner. Below the title was the phrase **'Working to eradicate the patient impact of COPD & asthma'** followed by 'Taking a **patient-centred** approach to deliver **a range of medicines to enable clinicians** to tailor treatment to patients' needs'. Beneath this was a text box that included the following: 'We are delighted to be able to support and be in attendance at this year's winter BTS Meeting'. Followed by 'Come and talk to us on our exhibition stands: ....'. Stand numbers and details of their location were provided as well as contact details for further information.
The Panel noted GlaxoSmithKline's submission that the purpose of the flyer was to highlight its support and corporate presence at the Winter 2013 Meeting of the British Thoracic Society. The flyer clearly encouraged visiting the company's exhibition stands including the promotional stands.

The Panel noted GlaxoSmithKline's submission that in Case AUTH/1920/11/06 the Panel had accepted a corporate mission statement in a therapy area to be non-promotional in the absence of a specific product claim and in Case AUTH/2216/3/09 the Panel accepted a corporate logo and strapline to be independent from a product claim when there was sufficient separation between the two. The Panel considered that there were significant differences between these cases and that presently at issue. The Panel noted that each case was judged on its own merits.

Turning to the present case, Case AUTH/2681/11/13, the Panel considered that in certain circumstances a corporate mission statement might be regarded as promotional: both its content and context were relevant factors. The Panel noted GlaxoSmithKline's submission that the flyer did not refer specifically to any GlaxoSmithKline product and that it was created with its corporate branding rather than product-specific branding. However, the Panel noted that the flyer was an invitation to visit, *inter alia*, GlaxoSmithKline's promotional stands and mentioned COPD and asthma.

The Panel noted GlaxoSmithKline's full corporate mission statement: 'to improve the quality of human life by helping people to do more, feel better and live longer'. The Panel considered that the abridged mission statement 'do more, feel better, live longer' as it appeared on the flyer in question was different. Context was also important.

The abridged mission statement appeared on a flyer which referred to GlaxoSmithKline respiratory and the patient impact of COPD and asthma and invited attendance at, *inter alia*, three promotional stands. Whilst the Panel accepted that 'do more' might be considered a statement of general corporate intent, 'feel better, live longer', within the context of an item headed GlaxoSmithKline respiratory and which referred to eradication of the patient impact of COPD and asthma, could refer to the effect of GlaxoSmithKline's respiratory product portfolio. Indeed this was the view of the complainant. In this regard the Panel noted that whilst the phrase in question was physically separate from the main body of text, visually it had the same colour font and font style as the rest of the item and appeared to be an integral part of the whole. The Panel thus considered on balance, within the context of this particular item, that the phrase in question was a claim for GlaxoSmithKline's respiratory portfolio, including Seretide.

The Panel noted that the complainant had the burden of proving his complaint on the balance of probabilities. The Panel noted the complainant's allegation that the claim 'do more, feel better, live longer' implied, *inter alia*, that Seretide could make you live longer. According to the complainant the TORCH study did not support this. The Panel considered that the claim was thus misleading in relation to Seretide and a breach of Clause 7.2 was ruled.

The Panel noted its finding above that the phrase 'do more, feel better, live longer' was a claim for GlaxoSmithKline's respiratory portfolio. However the complainant had submitted no material and referred to no evidence to support his position in relation to the rest of the medicines in GlaxoSmithKline's respiratory portfolio. The Panel noted that the complainant bore the burden of proof and considered that he had not established his case on the balance of probabilities. Whilst the Panel was concerned about the phrase in question, in the absence of any evidence on this point and on this narrow ground alone the Panel did not consider the claim misleading or all embracing in relation to the rest of GlaxoSmithKline' respiratory portfolio. No breach of Clauses 7.2 and 7.10 was ruled.

APPEAL FROM GLAXOSMITHKLINE

GlaxoSmithKline strongly disagreed with the Panel's ruling that the corporate mission 'do more, feel better, live longer' was a claim for its respiratory portfolio, including Seretide. The company noted that the Panel ruled no breach in relation to the mission statement being a claim for its respiratory portfolio (excluding Seretide), as the complainant had not provided any material or evidence to support his position in this context. Nonetheless, it was not clear from the Panel's ruling or from the original complaint, why the corporate mission statement 'do more, feel better, live longer' was linked with Seretide as no evidence had been provided to establish such a connection.

GlaxoSmithKline appealed the ruling of a breach of Clause 7.2 on the grounds that 'do more, feel better, live longer' was not a claim and in that regard it noted that the corporate mission was created when GlaxoWellcome and SmithKlineBeecham merged in 2001. 'At GSK, our mission is to improve the quality of human life by enabling people to do more, feel better, live longer', with an abbreviated form 'do more, feel better, live longer'. This mission encompassed all of GlaxoSmithKline's divisions, including research & development, pharmaceuticals, vaccines and consumer health. This mission statement had been used as a strapline on the front cover of official documents such as the Annual Report and the Corporate Responsibility Report (images provided). This strapline along with GlaxoSmithKline's logo had also been used extensively on the title page and/or front slide of external presentations by the GlaxoSmithKline leadership team. The corporate mission also underpinned GlaxoSmithKline's values and behaviours and so it also featured on the internal Code of Conduct. GlaxoSmithKline noted that the complainant acknowledged that the strapline referred to GlaxoSmithKline's aspiration and that it was appropriate.

GlaxoSmithKline therefore submitted that the invitation stated its corporate commitment to contributing to improving the health of patients and was not a claim. As such, it fell outside the scope of Clause 7.2 of the Code.

GlaxoSmithKline also appealed the Panel's ruling on the grounds that there was inadequate evidence to support the allegation that the corporate mission was linked to Seretide and in that regard noted that the Constitution and Procedure stipulated that the complainant had the burden of proving their complaint on the balance of probabilities. It was not evident from the complaint or from the Panel's assessment how the complainant had established an association between the corporate mission statement 'do more, feel better, live longer' on the invitation and Seretide.

GlaxoSmithKline submitted that in October 2013, before it received this complaint, new internal guidance was issued on the use of the corporate mission which clearly outlined that the strapline should not be used on any external communications or materials, including emails, detail aids, meeting slides etc where the content related to a medicine, vaccine or consumer product. GlaxoSmithKline UK staff were given this global guidance (email provided) to ensure that the corporate mission strapline would not be misconstrued as a product-specific promotional claim.

GlaxoSmithKline submitted that the invitation at issue was created in line with the internal guidance. There was no reference to any medicine. The corporate logo and strapline were positioned in the top right-hand corner to ensure they were sufficiently separated from the main body of the text, distinguishing this as a corporate mission. Furthermore, the invitation was specifically created with corporate branding (bright orange) rather than any product-specific branding. In that regard GlaxoSmithKline noted that Seretide had a distinctive purple branding (promotional materials were provided) which had been used over the last 14 years and would be familiar to respiratory physicians since Seretide had been the market leader in its class over the last decade. GlaxoSmithKline had no reason to believe that the bright orange corporate branding would ever be confused with or mislead towards Seretide by a health professional. Finally, the exhibition stands at the winter BTS meeting promoted Relvar Ellipta, a recently licensed respiratory medicine which carried a light blue and grey branding; Seretide was not promoted at these stands.

GlaxoSmithKline therefore asserted that there was inadequate evidence to establish a link between the corporate mission stated on the invitation and Seretide.

GlaxoSmithKline also noted that in Case AUTH/2216/3/09 the Panel had ruled that a corporate logo and strapline ('deliver more') was not a claim despite its appearance on promotional material which referred to a specific product; the Panel concluded that there was sufficient separation between the product logo and corporate logo. In addition, in Case AUTH/1920/11/06 the Panel considered the corporate mission 'you need to be able to count on the company that supplies your medicine' on disease awareness campaign materials directed at public to be non-promotional since no product-specific claim was made. GlaxoSmithKline submitted that the facts of these two cases were relevant to the present case.

Finally, GlaxoSmithKline appealed on the basis that 'do more, feel better, live longer' could be substantiated and submitted that if the PMCPA wished to consider the case on the narrow point on which it had ruled, notwithstanding the above, as quoted by the complainant, GlaxoSmithKline had supported respiratory medicine over the years and had brought several medicines to the bedside in order to address patients' needs in this therapy area. For example, Ventolin (salbutamol sulphate) still formed a significant part of GlaxoSmithKline's respiratory portfolio. Ventolin was a 'rescue' medicine for chronic asthma patients in order to treat as well as prevent asthma exacerbations which carried a significant risk of mortality. Ventolin had also been recommended by guidelines as the initial therapy for life-threatening acute asthma attacks (British Guideline on the Management of Asthma: A national clinical guideline, May 2008, Revised January 2012).

GlaxoSmithKline submitted that it was generally accepted that Ventolin had saved lives over the years especially in the acute care setting. Therefore, the complainant's allegation 'none of the GlaxoSmithKline respiratory products make you live longer' was factually incorrect. Furthermore, whilst GlaxoSmithKline acknowledged the complainant's argument that the TORCH study did not show reduced mortality with Seretide, an independent Cochrane review published in November 2013 concluded there was significant reduction in mortality with Seretide compared with placebo when the results of TORCH study were pooled with data from other studies (Nannini *et al* 2013). In addition, GlaxoSmithKline's portfolio of medicines could be shown to support the abridged mission statement of 'do more, feel better, live longer'.

GlaxoSmithKline submitted that the use of the abridged mission statement coupled with the GlaxoSmithKline's logo on the invitation, which did not refer to any medicine, was use of its corporate logo and did not constitute a claim for its respiratory portfolio including Seretide. As such, the invitation did not breach Clause 7.2 of the Code.

COMMENTS FROM THE COMPLAINANT

The complainant reiterated that in his view the invitation was confusing because when taken in conjunction with the corporate logo, which contained the phrase 'feel better, live longer', it might be interpreted in relationship to GlaxoSmithKline's market leading product, Seretide. The Panel did not support the complaint in relation to the other products in GlaxoSmithKline respiratory portfolio since he had not provided evidence to support this contention. The complainant understood that he must provide the balance of evidence, however it was perhaps a little unreasonable to expect someone to comprehensively review the published literature concerning all of the respiratory products in the market leading pharmaceutical company in this therapeutic area. The complainant had therefore restricted his review to the eMC list of GlaxoSmithKline respiratory products. The summaries of product characteristics claimed symptomatic relief only and made no claims concerning longevity. The complainant was unaware of any published evidence which would support any such claims.

The complainant therefore alleged that the use of the corporate strapline on an invitation to discuss the respiratory portfolio inferred a claim which was not substantiated by the published evidence. Had, as the Panel suggested, the previous approved corporate strapline been clearly distinguished, either through colour or some other typographical mechanism, then the complainant would have no problem with its use. Such corporate aspirations were indeed laudable. It was the close conjunction which might have confused the complainant's colleagues which was the problem.

APPEAL BOARD RULING

The Appeal Board acknowledged that in certain circumstances a corporate statement might be regarded as promotional.

The Appeal Board noted that the bright orange invitation/flyer at issue was entitled 'GSK Respiratory' and in the top right-hand corner next to the GlaxoSmithKline corporate logo was the strapline 'do more, feel better, live longer'. The Appeal Board considered the positioning of the strapline to the right of the logo, and therefore on the outer right edge of the invitation, separated it from the body of the invitation. The invitation/flyer advised that GlaxoSmithKline would support and attend the winter BTS meeting and it invited readers to visit the company's promotional and medical exhibition stands. In that regard the Appeal Board noted GlaxoSmithKline's submission that its promotional stands at the meeting promoted Relvar Ellipta and not Seretide.

The Appeal Board further noted that within GlaxoSmithKline orange was reserved for corporate branding; it was not linked to a promoted product. The Appeal Board noted that the invitation did not mention any specific medicines. The Appeal Board considered that the strapline 'do more, feel better, live longer' as it appeared in the top right-hand of the invitation/flyer in question did not relate to, or make any claims for, any particular medicine, including Seretide. The Appeal Board ruled no breach of Clause 7.2. The appeal was successful.

Complaint received **25 November 2013**

Case completed **19 February 2014**

CASE AUTH/2682/11/13

ANONYMOUS v MERCK SERONO

Provision of Hospitality

An anonymous and non-contactable complainant who described themselves as a fertility health professional submitted a complaint about the provision of hospitality by Merck Serono.

The complainant stated that Merck Serono had flown delegates premium class to an international conference in Boston and during the conference had hosted lavish dinners followed by drinks parties that went on into the early hours of the morning and during which large amounts of alcohol were consumed.

The complainant alleged that this excessive level of hospitality was further evidenced by Merck Serono's conduct at another international conference in London during which it entertained UK health professionals on a Thames river boat cruise with music, and treated them to an extravagant gala dinner held in the Tower of London where an excessive amount of alcohol was provided.

The detailed response from Merck Serono is given below.

The Panel noted that as the complainant was anonymous and non-contactable it was not possible to ask the complainant for further information. The Panel noted that Merck Serono had provided a detailed account of subsistence provided during both conferences.

The Panel noted that the Code required that companies should only offer or provide economy air travel to delegates sponsored to attend meetings. Delegates could of course organise and pay at their own expense the genuine difference between economy travel and business class or first class. The Panel noted that the reference to economy air travel first appeared in the 2006 Code and that airlines' offerings in relation to class of travel had developed since then.

The Panel noted that PMCPA advice stated that developments in recent times had led to classes of travel being offered which included 'economy' in their title such as premium economy and were part way between economy and business class. It was unlikely that the payment of a significantly more expensive fare than economy would ever be acceptable under the Code. The PMCPA's view was that the use of economy tickets put companies beyond reproach. The Panel thus considered that perception and cost were important factors when deciding whether premium economy flights were acceptable. There was no mention in either the Code or the published advice that the length of travel was a relevant factor.

The Panel noted that airlines' offerings differed. Some airlines offered economy, premium economy and upper class flights and therefore premium economy might be considered a version of business class. Other airlines offered economy, world traveller plus, business and first class flights so world traveller plus might be considered to be part way between economy and business class. The matter was further complicated as airlines used different terms to describe similar levels of service.

The Panel noted Merck Serono's submission that the cost per premium economy ticket for delegates to attend the meeting was £1250. The Panel assumed that this also applied to the world traveller plus tickets. The Panel noted that one delegate travelled economy class from Ireland to Boston. The Panel noted that Merck Serono could not provide the actual cost of economy flights for the specific dates travelled. Instead Merck Serono provided the cost for flights to Boston on a Saturday and returning on a Thursday booked approximately six weeks in advance. The Panel noted that these were such that the actual cost of premium economy and world traveller plus flights were significantly more expensive than the corresponding economy flights. However, it was entirely unclear whether these economy flight costs were closely similar to the costs which would have been incurred had economy class tickets been booked originally. It was thus not possible to determine whether the premium economy class tickets and world traveller plus tickets purchased were significantly more expensive than the corresponding economy flights. The Panel was, nonetheless, extremely concerned about the impression given. The Panel also noted the impression that one airline's offering of premium economy appeared to be akin to business class. The Panel considered that on the evidence before it the provision of a class of flight other than economy was contrary to the Code and a breach was ruled.

The Panel noted that the American Society for Reproductive Medicine (ASRM) conference lasted from Saturday, 12 October to Thursday, 17 October 2013. The Panel considered that the subsistence provided to the Merck Serono delegation on 13–15 October at local restaurants was not unreasonable. Costs incurred varied from £35 to £40 per head including drinks. The Panel ruled no breach of the Code.

The Panel noted that the restaurant that Merck Serono had originally intended to go to on Wednesday, 16 October had to be changed on the evening as its staff refused to serve any delegates who did not have their passports with them. Merck Serono submitted that a steak house was the only available venue for a large number of diners at short notice. The cost per head including drinks was £83 which Merck Serono acknowledged was higher than it would ordinarily consider acceptable.

The Panel considered that the circumstances in this regard were unusual. In the Panel's view Merck Serono should have been aware that the booked restaurant required diners to bring their passports. It was important for a company to be mindful of the impression created by its activities; this was especially so in relation to the provision of subsistence in a public restaurant irrespective of the circumstances. The Panel considered that the cost was such that the subsistence provided to the health professionals was contrary to the Code and a breach was ruled. The Panel did not consider that, given the exceptional circumstances of this case, Merck Serono had failed to maintain high standards and no breach of the Code was ruled. The Panel consequently ruled no breach of Clause 2.

The Panel noted Merck Serono's submission that no hospitality was provided to any health professionals by Merck Serono following the dinners nor did Merck Serono employees accompany any delegates to any bars or clubs. The Panel did not consider that the complainant had proved on the balance of probabilities that Merck Serono had hosted lavish drinks parties that went on until the early hours of the morning and during which large amounts of alcohol were consumed as alleged. No breach of the Code was ruled.

The Panel noted that the European Society of Human Reproduction and Embryology (ESHRE) conference lasted from Sunday, 7 July to Wednesday, 10 July 2013.

The Panel noted the costs per head for the dinner on 7 July at a hotel was £42 and 8 July at a restaurant was £30. The Panel did not consider that the subsistence provided on either occasion was unreasonable and ruled no breach of the Code in relation to each.

The Panel was concerned that on the 8 July, three Merck Serono employees accompanied forty health professionals to a patient organisation's 10th anniversary event held on a river boat cruise along the Thames. The Panel noted Merck Serono's submission that it had no input into the organisation of this event and had not provided any financial support for the event. Merck Serono had at the request of the patient organisation notified its delegation of the event. The Panel noted Merck Serono's submission that no drinks were purchased by Merck Serono employees either for invited delegates or for personal consumption. Merck Serono had not paid for any aspect of the event including any hospitality. The Panel thus ruled no breach of the Code in that regard.

In relation to the river boat cruise, the Panel queried whether it was appropriate for Merck Serono employees to accompany its delegates to an event that appeared to be entirely social in nature. It was likely that attendees would be attracted by the venue. It was important for a company to be mindful of the impression created by its activities. The Panel considered that the impression given by the presence of Merck Serono employees with health professional delegates on the river boat which was likely to be more of a party atmosphere was wholly unacceptable. In that regard the Panel considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted the cost per head for dinner on 9 July at a restaurant was £68 including £14 per head for wine and mineral water. That it was possible to provide subsistence in the evening at a central London venue at a lower cost was evidenced by the cost of the meal at the restaurant on 8 July. The Panel considered that the hospitality was on the upper limits of acceptability. It was concerned about the impression given by the arrangements. The Panel decided on the evidence before it that the hospitality, on balance was not unacceptable. The attendees were health professionals and the main purpose of the conference was educational. No breach of the Code was ruled.

The Panel decided the circumstances in this case were not such as to bring discredit upon and reduce confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

An anonymous non-contactable complainant who described themselves as a fertility health professional submitted a complaint about the provision of hospitality by Merck Serono.

COMPLAINT

The complainant stated that most recently delegates were flown premium class to an international conference, the American Society for Reproductive Medicine (ASRM) in Boston. During this conference two Merck Serono senior managers hosted lavish dinners for UK health professionals which were followed by drinks parties that went on into the early hours of the morning and during which large amounts of alcohol were consumed.

The complainant alleged that this excessive level of hospitality was typical of Merck Serono and was further evidenced by its conduct at another international conference, European Society of Human Reproduction and Embryology (ESHRE) in London. During this conference UK health professionals were entertained by Merck Serono on a Thames river boat cruise with music, and on the following night they were treated to an extravagant gala dinner held in the Tower of London where an excessive amount of alcohol was provided.

The complainant alleged that this lavish hospitality was entirely inappropriate and responsible for bringing the pharmaceutical industry and the health profession into disrepute.

When writing to Merck Serono, the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Merck Serono was very disappointed to receive a complaint in relation to its activities at ASRM and the ESHRE meetings. Merck Serono submitted that it took its obligations under the Code very seriously.

1 American Society for Reproductive Medicine annual meeting

This congress was held in Boston, US from 12-17 October 2013 and attendance by Merck Serono was organised by the Head of Fertility, UK & Ireland. In total, the Merck Serono delegation to this congress comprised of 12 delegates, 10 of whom were health professionals and two of whom were Merck Serono employees.

As the delegation was limited there was no specific briefing for ASRM. A briefing in relation to hospitality etc was provided before the ESHRE annual meeting in July and Merck Serono considered that this briefing was sufficient to cover the ASRM meeting. An email regarding provision of hospitality sent to the whole company in September following a ruling by the PMCPA and which reflected the company's responsibilities to the Code was provided.

Merck Serono submitted that the support provided by Merck Serono to health professionals was registration fees, flights and/or accommodation. The itinerary provided details for each health professional and noted that all flights were either economy class or premium economy in line with the requirements of Clause 19.1. With regard to accommodation, all Merck Serono delegates stayed at a hotel chosen due it its proximity to the conference venue at the Boston Convention and Exhibition Centre. For some of the delegates the departure date was not immediately after the conclusion of the meeting, and for some the departure was not from Boston airport. This was because some delegates had other business in the US but Merck Serono only paid for accommodation for the duration of the ASRM meeting and did not pay for any internal flights in the US.

Merck Serono organised dinners on the nights of 13-16 October as set out below and copies of the receipts were provided.

Sunday, 13 October 2013

This dinner was attended by 16 delegates, plus two Merck Serono employees. Five of the 16 health professionals were part of the Merck Serono delegation. The others, though not supported by Merck Serono to attend the congress, were UK delegates at the congress and had attended the educational sessions that had taken place that day. The cost per head for this dinner (including drinks) was $65.65, approximately £40 per head. Merck Serono submitted that this was not excessive or extravagant and was in line with Merck Serono's meetings and hospitality standard operating procedure (SOP) which allowed up to £45 per head for dinner. The receipt was issued at 9.50pm.

Monday, 14 October 2013

This dinner was attended by two Merck Serono employees and six health professionals, five of whom were part of the Merck Serono delegation. The other health professional, though not supported by Merck Serono to attend the congress, was a UK delegate at the congress and had attended the educational sessions that had taken place that day. The cost per head for this dinner (including drinks) was $56.97, approximately £35 per head. Merck Serono submitted that this was not excessive or extravagant and was in line with Merck Serono's meetings and hospitality SOP. The receipt was issued at 10.09pm.

Tuesday, 15 October 2013

This dinner was attended by two named Merck Serono employees and 15 health professionals, five of whom were part of the Merck Serono delegation. The other health professionals, though not supported by Merck Serono to attend the congress, were UK delegates at the congress and had attended the educational sessions that had taken place that day. The cost per head for this dinner (including drinks) was $61.16, approximately £37 per head. Merck Serono submitted that this was not excessive or extravagant and was in line with Merck Serono's meetings and hospitality SOP. The receipt was issued at 10.34pm.

Wednesday, 16 October 2013

This venue was not the one that Merck Serono planned to take its delegation to. The original restaurant had to be changed on the evening of the meal,due to restaurant staff refusing to serve any delegates who did not have their passport with them, to a steak house, which was the only venue available for a large number of diners at short notice. This dinner was attended by two Merck Serono employees and 12 health professionals, four of whom were part of the Merck Serono delegation. The other health professionals, though not supported by Merck Serono to attend the congress, were delegates at the congress and had attended the educational sessions that had taken place that day. The cost per head for this dinner (including drinks) was $135.93, approximately £83 per head. Merck Serono recognised that this cost per head was higher than it would ordinarily consider acceptable, however, as noted above, this was the only venue available at short notice during conference week. The receipt was issued at a slightly later time than the other evenings, 11.40pm, reflecting the need to change restaurant.

In addition to the dinners noted above, subsistence was purchased at Heathrow airport on 12 October for two health professionals who were part of the Merck Serono delegation and the two named Merck Serono employees. The cost per head was £13.06, which was in line with Merck Serono's meetings and hospitality SOP (£25 per head for a restaurant lunch and £18 per head for a buffet).

Given the above, Merck Serono submitted that the hospitality provided at ASRM was appropriate and not out of proportion to the occasion. The costs involved did not exceed the level which the recipients would normally adopt when paying for themselves. Merck Serono had complied with the requirements of Clause 19.1 and refuted the allegation of a breach of that Clause in relation to

hospitality provided at ASRM. Consequently there was no breach of Clauses 9.1 and 2.

In response to a request for information from the case preparation manager, Merck Serono submitted that no hospitality was provided to any health professionals by Merck Serono following the dinners nor did Merck Serono employees accompany delegates to any bars or clubs or go to such venues on their own. Following dinner each night, Merck Serono employees returned to their hotel and retired for the evening.

In response to a request for further information from the Panel Merck Serono submitted that the delegation to the American Society for Reproductive Medicine was offered varying levels of support which ranged from travel, registration and accommodation to registration and/or accommodation. Six delegates had the full package, including flights. Four delegates had registration and/or accommodation but paid for their own travel which was why flight details were not included. Premium economy and world traveller plus flights were selected as the classes were included in Merck Serono's company policy for flights over five hours.

The cost paid by Merck Serono per ticket for the flight to this meeting was £1250 (premium economy). Merck Serono did not have the details of the cost of the economy flights for the specific dates that health professionals travelled to the ASRM. However, having checked the airlines' websites for return seats to Boston departing on a Saturday and returning on a Thursday (as was the case for ASRM delegates) if booked approximately 6 weeks before travel, Merck Serono provided the following costs:

First airline economy: £532.75 (lowest) to £1534.75 (fully flexible)
First airline world traveller plus: £935.75 (lowest) to £2, 291.75 (fully flexible)

Second airline economy: £457.75 (lowest) to £1534.25 (fully flexible)
Second airline premium economy: £838.25 (lowest) to £2366.25 (fully flexible)

Merck Serono considered that the flights provided to health professionals attending ASRM were appropriate, given the length of travel time, were in line with the requirement in the supplementary information to Clause 19.1 and were certainly not excessive hospitality as alleged by the complainant.

In relation to the four health professionals who did not depart immediately after the conclusion of ASRM, all paid for their own internal flights. One health professional travelled at her own expense to New York to visit a colleague's clinic there and travelled back to the UK from New York. The return cost of travelling back from New York instead of Boston was the same as if she had travelled back from Boston.

Another health professional travelled at her own expense to Washington to visit colleagues and to attend a meeting related to a fertility society and travelled back to the UK from Washington. Again, the price of the fare was the same as if she had flown back from Boston.

A further health professional travelled at his own expense from Boston to Indianapolis, from Indianapolis to Chicago and then travelled back from Chicago to Manchester. This was for personal reasons. There was no additional cost to Merck Serono for this travel.

The fourth delegate stayed on to attend part of the congress at the end of the program and she would have missed this to get the flight to Dublin on Thursday 17 October. Merck Serono covered her accommodation for Thursday night for this reason and she flew back to Dublin on the Friday. There was no additional flight cost for the travel back on Friday.

In response to a request for further information from the Panel Merck Serono submitted that it had contacted both airlines and neither held retrospective flight costs. Merck Serono submitted that apparently they fluctuated depending on several factors and the comment from one airline was that it would be unable to give a precise cost for a flight booked in the preceding days. Merck Serono submitted that unfortunately the information did not exist and therefore could not be provided.

2 European Society of Human Reproduction and Embryology annual meeting

The conference was held at ExCel, London 7-10 July 2013. Attendance by Merck Serono at this meeting was organised by the Head of Fertility, UK & Ireland. In total, the Merck Serono delegation to this congress comprised of 65 delegates, 53 of whom were health professionals and 12 of whom were Merck Serono employees. The support provided by Merck Serono to health professionals was registration fees, subsistence and/or accommodation.

A copy of the briefing presentation to Merck Serono delegates before attending the meeting was provided.

The accommodation for the Merck Serono delegation was chosen because of the location within walking distance of the Docklands Gateway. This enabled convenient access to the ExCel centre by the docklands light railway (DLR). Merck Serono organised dinners on the nights of 7-9 July. All meals were pre-booked and paid for in advance.

Sunday, 7 July

A meal was provided once delegates had arrived at the hotel they were staying at during the conference.

Monday, 8 July

On the same night, a patient organisation held an event to celebrate its 10th anniversary on a river boat on the Thames. Merck Serono had no input

in to its organisation and did not provide any financial support. At the request of the patient organisation, Merck Serono notified its delegation of the event and some attended this instead of the meal at a restaurant organised by Merck Serono. The invitation from the patient organisation and the function sheet for the event was provided.

Tuesday, 9 July

The cost of the meal at this event was £68 per head. This was above what Merck Serono would usually deem acceptable, it was considered acceptable by exception, given that this was a dinner at major conference. The cost per head for wines and mineral water was £14.00 which could not be considered 'an excessive amount of alcohol' as alleged.

Merck Serono submitted that the information provided demonstrated that the company did not provide the level of hospitality alleged by the complainant and was compliant with Clause 19.1.

The Merck Serono staff had passed the ABPI representatives examination.

In response to a request from the case preparation manager for further information, Merck Serono confirmed that following the dinners no hospitality was provided by Merck Serono to any health professional. The Merck Serono employees did not accompany any delegates to any bars/clubs etc nor did they go to any such venues on their own. They returned to their hotel and retired for the evening. Given this, there were no receipts etc.

A briefing in relation to hospitality etc was provided before the ESHRE annual meeting in July.

In response to a request for further information Merck Serono provided details of the dinner attendance at the European Society of Human Reproduction and Embryology as follows:

Date	HCP attendees	Merck Serono attendees
7 July	52	7
8 July	36	4
8 July, Riverboat	40	3
9 July	93	11

All health professional attendees were Merck Serono delegates who had support for registration and/or accommodation. Three Merck Serono employees attended the patient organisation riverboat cruise but no drinks were purchased by Merck Serono employees either for invited delegates or for personal consumption. Any appropriate purchases would have been claimed on expenses and no expense claims had been made relating to the riverboat event.

In response to a request for further information from the Panel, Merck Serono submitted that it had provided 53 delegates with a full package including accommodation and registration for the European Society of Human Reproduction and Embryology annual meeting. As the meeting was in London there were a number of delegates who did not require accommodation and Merck Serono provided 41 delegates with congress registration only. These delegates were also invited to the dinner on 9 July which accounted for the difference between the numbers previously submitted.

PANEL RULING

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

Clause 19.1 stated that hospitality must not be provided except in association with, *inter alia*, scientific congresses, meetings and promotional meetings. Hospitality must be strictly limited to the main purpose of the event and must be secondary to the purpose of the meeting ie subsistence only. The level of subsistence offered must be appropriate and not out of proportion to the occasion. The costs involved must not exceed that level which the recipients would normally adopt when paying for themselves. The supplementary information to Clause 19.1 made it clear that the provision of hospitality was limited to subsistence, accommodation, genuine registration fees and the payment of reasonable travel costs which a company might provide to sponsor a delegate to attend a meeting. The venue must not be lavish, extravagant or deluxe and companies must not sponsor or organise entertainment such as sporting or leisure events. Meetings for health professionals etc which were wholly or mainly of a social or sporting nature were unacceptable. In determining whether a meeting was acceptable or not consideration needed to be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, subsistence provided and the like. It should be the programme that attracted delegates and not the associated hospitality or venue. The supplementary information also stated that a useful criterion in determining whether the arrangements for any meeting were acceptable was to apply the question 'would you and your company be willing to have these arrangements generally known?' The impression that was created by the arrangements for any meeting must always be kept in mind.

The Panel noted that the complainant alleged that Merck Serono provided extravagant levels of hospitality to UK health professionals citing examples of flying delegates premium class to the ASRM conference in Boston and providing lavish dinners and drinks parties in relation to this congress and a Thames riverboat cruise and gala dinner at the Tower of London in relation to the ESHRE conference. The Panel noted that Merck Serono had provided a detailed account of subsistence provided during both conferences.

ASRM

The Panel noted that the ASRM conference lasted from Saturday, 12 October to Thursday, 17 October 2013.

The supplementary information to Clause 19.1 stated that companies should only offer or provide economy air travel to delegates sponsored to attend meetings. Delegates may of course organise and pay at their own expense the genuine difference between economy travel and business class or first class. The Panel noted that the reference to economy air travel first appeared in the 2006 edition of the Code and that airlines' offerings in relation to class of travel had developed since then.

The Panel noted that PMCPA advice, Air Travel, stated that developments in recent times had led to classes of travel being offered which included 'economy' in their title such as premium economy and were part way between economy and business class. It was unlikely that the payment of a significantly more expensive fare than economy would ever be acceptable under the Code. The advice stated that the PMCPA's view was that the use of economy tickets put companies beyond reproach. The Panel thus considered that perception and cost were important factors when deciding whether premium economy flights were acceptable. This was the first time the Panel had to consider a complaint which related to the class of air travel. There was no mention in either the Code or the published advice that the length of travel was a relevant factor.

The Panel noted that airlines' offerings differed. Some airlines offered economy, premium economy and upper class flights and therefore premium economy might be considered a version of business class. Other airlines offered economy, world traveller plus, business and first class flights so world traveller plus might be considered to be part way between economy and business class. The matter was further complicated as airlines used different terms to describe similar levels of service.

The Panel noted Merck Serono's submission that the cost per premium economy ticket for delegates to attend the meeting was £1250. The Panel assumed that this also applied to world traveller plus tickets. The Panel noted that one delegate travelled economy class from Ireland to Boston. The Panel noted that Merck Serono could not provide the actual cost of economy flights for the specific dates that health professionals travelled to the ASRM as the airlines concerned did not hold details of retrospective flight costs. Instead Merck Serono provided the cost for flights to Boston on a Saturday and returning on a Thursday booked approximately six weeks in advance. The Panel noted that these were such that the actual cost of the premium economy and world traveller plus flights were significantly more expensive than the corresponding economy flights. However, it was entirely unclear whether the costs of these economy flights were closely similar to the costs which would have been incurred had economy class tickets been booked originally. It was thus not possible to determine whether the premium economy class tickets and world traveller plus tickets purchased were significantly more expensive than the corresponding economy flights. The Panel was, nonetheless, extremely concerned about the impression given. The Panel also noted the impression that one airline's offering of premium economy appeared to be akin to business class. The Panel considered that on the evidence before it the provision of a class of flight other than economy was contrary to Clause 19.1 and a breach of that clause was ruled.

The Panel noted the complainant's allegation that two named company employees had provided lavish dinners followed by drinks parties.

The Panel noted that there were a number of health professionals present at the dinners who were not part of the Merck Serono delegation. The Panel understood that such meals were often booked and paid for in advance and some attendees might drop out. In order to prevent wastage, pharmaceutical companies might invite alternative delegates that they had not originally sponsored to fill these spaces. The Panel considered that the number of places a pharmaceutical company booked for dinner should generally be proportionate to the number of its delegates. The Panel noted that the scientific content of the ASRM would have been the same for all delegates but queried why there were more non delegates than delegates present at the majority of the Merck Serono dinners. The Panel considered that it might not be unreasonable for a company to provide subsistence to health professionals attending a congress who were not sponsored by that company. In such situations the company would be well advised to be able to show that the health professional had attended the educational sessions that had taken place that day. Any such arrangements had to comply with the Code. The Panel noted that it did not have a specific complaint about this aspect and thus little information from Merck Serono about it. The Panel made no ruling on this point.

The Panel considered that the subsistence provided to the Merck Serono delegation on 13–15 October at local restaurants was not unreasonable. Costs incurred varied from £35 to £40 per head including drinks. The Panel ruled no breach of Clause 19.1.

The Panel noted that dinner on Wednesday, 16 October was attended by the two Merck Serono employees and twelve health professionals, four of whom were part of the Merck Serono delegation and eight who were not supported by Merck Serono to attend the congress but were UK delegates who Merck Serono submitted had attended the educational sessions that had taken place that day. The Panel noted that the restaurant that Merck Serono had originally intended to go to had to be changed on the evening as its staff refused to serve any delegates who did not have their passports with them. Merck Serono submitted that a steak house was the only available venue for a large number of diners at short notice. The cost per head including

drinks was £83 which Merck Serono acknowledged was higher than it would ordinarily consider acceptable and the receipt had been issued at 11.40 pm, slightly later than normal reflecting the need to change restaurants.

The Panel considered that the circumstances in this regard were unusual. In the Panel's view Merck Serono should have been aware that the booked restaurant required diners to bring their passports. It was important for a company to be mindful of the impression created by its activities; this was especially so in relation to the provision of subsistence in a public restaurant irrespective of the circumstances. The Panel considered that the cost was such that the subsistence provided to the health professionals at the steak house was contrary to Merck Serono's SOP and the requirements of Clause 19.1 and a breach of that clause was ruled. The Panel did not consider that, given the exceptional circumstances of this case, a ruling of a breach of Clause 9.1 was warranted and no breach of that clause was ruled. The Panel consequently ruled no breach of Clause 2.

The Panel noted Merck Serono's submission that no hospitality was provided to any health professionals by Merck Serono following the dinners nor did Merck Serono employees accompany any delegates to any bars or clubs. The Panel did not consider that the complainant had proved on the balance of probabilities that Merck Serono had hosted lavish drinks parties that went on until the early hours of the morning and during which large amounts of alcohol were consumed as alleged. No breach of Clause 19.1 was ruled in that regard.

ESHRE

The Panel noted that the ESHRE conference lasted from Sunday, 7 July to Wednesday, 10 July 2013.

The Panel noted that the Merck Serono SOP Meetings, Subsistence and Associated Allowable Expenditure stated that one glass of wine per person was allowed with dinner. However, an email regarding the provision of hospitality at conferences stated that subsistence could be provided in association with appropriate meetings usually included up to half a bottle of wine per person and that was what was provided in most cases.

The Panel noted that dinner on 7 July was attended by fifty nine people, including fifty two health professionals and seven Merck Serono employees and the cost per head including drinks was £42. The Panel noted that dinner on 8 July was attended by thirty six health professionals and four Merck Serono employees. The cost per head was £30. The Panel did not consider that the subsistence provided on either occasion was unreasonable and ruled no breach of Clause 19.1 in relation to each event.

The Panel was concerned that on the same night, 8 July, three Merck Serono employees accompanied forty health professionals to a patient organisations 10th anniversary event held on a river boat cruise along the Thames. The Panel noted Merck Serono's submission that it had no input into the organisation of this event and had not provided any financial support for the event. Merck Serono had at the request of the patient organisation notified its delegation of the event. The Panel noted Merck Serono's submission that no drinks were purchased by Merck Serono employees either for invited delegates or for personal consumption. Merck Serono had not paid for any aspect of the event including any hospitality. The Panel thus ruled no breach of Clause 19.1 in that regard.

In relation to the river boat cruise, the Panel queried whether it was appropriate for Merck Serono employees to accompany its delegates to an event that appeared to be entirely social in nature. It was likely that attendees would be attracted by the venue. It was important for a company to be mindful of the impression created by its activities. The Panel considered that the impression given by the presence of Merck Serono employees with health professional delegates on the river boat which was likely to be more of a party atmosphere was wholly unacceptable. In that regard the Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that dinner on 9 July at a restaurant was attended by ninety three health professionals and eleven Merck Serono employees. The cost per head was £68 including £14 per head for wine and mineral water. That it was possible to provide subsistence in the evening at a central London venue at a lower cost was evidenced by the cost of the meal at the restaurant on 8 July. The Panel considered that the hospitality was on the upper limits of acceptability. It was concerned about the impression given by the arrangements. The Panel decided on the evidence before it that the hospitality, on balance was not unacceptable. The attendees were health professionals and the main purpose of the conference was educational. No breach of Clause 19.1 was ruled.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The relevant supplementary information referred to excessive hospitality. The Panel decided the circumstances in this case were not such as to bring discredit upon and reduce confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

Complaint received **25 November 2013**

Case completed **15 April 2014**

EX EMPLOYEE v NOVO NORDISK

Conduct of company employees

An NHS associate director of commissioning and previously an employee of a company that provided services to pharmaceutical companies working with Novo Nordisk Pharmaceuticals in diabetes complained about the conduct of three Novo Nordisk employees. The complainant explained that he resigned from his previous position after six months due to the offensive behaviour of three named Novo Nordisk employees.

The complainant stated that he had recently been notified by two NHS diabetes specialist nurses that the three named Novo Nordisk employees had told them that he was dismissed from his role because a diabetes consultant and his/her secretary had each made a serious complaint about him and he had breached an internal standard operating procedure (SOP) regarding payment for a meeting. The complainant stated that these defamatory comments were entirely false and a totally unacceptable breach of the Code.

The detailed response from Novo Nordisk is given below.

The Panel noted that the complainant, who at the time of the complaint was an NHS associate director of commissioning, was formerly employed by a service provider working for Novo Nordisk. The complainant stated that he had resigned from his position but had been advised by two specialist NHS nurses that three named Novo Nordisk employees had told them that he had been dismissed for specific reasons. These reasons included that a diabetes consultant and his secretary had each made a serious complaint about him. The Panel noted that both the complainant and Novo Nordisk agreed that neither the diabetes consultant nor his secretary had made such a complaint.

The Panel noted that the complaint related to comments made by the Novo Nordisk employees to two NHS diabetes nurse specialists. The Panel noted the scope of the Code including that it applied to the promotion of medicines for prescribing to health professionals and appropriate administrative staff and to certain non promotional activities.

The Panel noted that as the complaint concerned what was allegedly said externally to health professionals about the reasons why the complainant had left his position including his conduct with other health professionals, it was a matter potentially covered by the Code.

The Panel noted that the complainant had to establish his case on the balance of probabilities.

The complainant had not identified the nurses in question nor provided any evidence to demonstrate that the comments at issue had, in fact, been made to the nurses in question. The signed statements submitted by Novo Nordisk for two of the three named employees each denied that they had notified NHS diabetes nurses that the complainant had been dismissed. Neither statement referred to a complaint about his conduct or a breach of an SOP. The Panel, therefore, considered that the complainant had not met the burden of proof and ruled no breach of the Code.

An NHS associate director of commissioning and previously an employee of a company that provided services to pharmaceutical companies working with Novo Nordisk Pharmaceuticals in diabetes complained about the conduct of three Novo Nordisk employees.

COMPLAINT

The complainant explained that prior to his current NHS senior management position, he was an employee of a service provider working with Novo Nordisk. The complainant stated that he resigned from the position after six months due to the offensive behaviour of three named Novo Nordisk employees.

The complainant stated that he had recently been notified by two NHS diabetes specialist nurses that three named Novo Nordisk employees had told them that he was dismissed from his role because a diabetes consultant and his secretary had each made a serious complaint about him and he had breached an internal standard operating procedure (SOP) regarding payment for a meeting The complainant considered that these defamatory comments were entirely false and a totally unacceptable breach of the Code.

The complainant had spoken directly to the diabetes consultant and his secretary and was assured that the allegations were total fabrication and no such conversations took place with any Novo Nordisk employee or anyone else. They were extremely offended that Novo Nordisk employees would implicate them in these false, defamatory allegations.

The complainant assumed that the SOP breach referred to related to a meeting in January/February 2013 which one of the named Novo Nordisk employees was responsible for breaching and then attempted to blame the complainant for his failure. The complainant stated that he had evidence which proved this.

The complainant stated that the comments made by the three named Novo Nordisk employees were blatantly untrue and slanderous. These false allegations could only have been made in order to tarnish the complainant's good name and reputation by individuals who had previously proven to have unjustified hostility towards him. The complainant was not prepared to tolerate this behaviour, or to have their actions damage his professional reputation.

Novo Nordisk was asked to respond in relation to Clauses 8.2, 9.1 and 15.2 of the Code.

RESPONSE

Novo Nordisk explained that the first Novo Nordisk employee was a sales representative who promoted medicines to health professionals in order to achieve territory product sales targets. The employee had left Novo Nordisk in 2013.

The second named Novo Nordisk employee managed a group of representatives. This employee was the manager of the first named Novo Nordisk employee.

The third named Novo Nordisk employee was a medical advisor who provided a medical advisory service.

The complainant was employed by a service provider and working on behalf of Novo Nordisk on market access matters. The complainant provided market access services to Novo Nordisk and reported to a manager.

The complainant and the three named Novo Nordisk employees had defined roles and were required to work collaboratively together within a region to meet business objectives.

In September 2013, various Novo Nordisk staff along with the compliance officer received an anonymous letter which was signed on behalf of a particular team. The author(s) of the letter made several allegations about members of the team, including the three employees named in this complaint and the allegations within that letter were broadly similar and related principally to internal employee/staff related matters. It was the view of all key stakeholders within Novo Nordisk that the complainant was the author of that letter.

A thorough investigation into the matter was conducted. This involved an interview with each of those referred to within the letter. The investigation did not substantiate any of the allegations made within it.

Novo Nordisk considered the content of the letter to be grossly defamatory against Novo Nordisk and the employees in question.

Novo Nordisk submitted that it subsequently received a further letter from the complainant. The allegations within that letter were broadly similar to those made within this complaint. Novo Nordisk responded by letter and copied in the managing directors of two NHS commissioning support units from whom Novo Nordisk had since received a response. The summary of the response was as follows:

> [The complainant] resigned from his position at NHS [named] …[in January 2014]; the managing director was unaware of the matters raised in his letter to Novo Nordisk [provided], despite the letter being sent on [named] headed paper and reassured Novo Nordisk that any relationship with Novo Nordisk and the NHS [named] was unaffected by the contents of the complainant's letter and confirmed that the complainant had been placed on garden leave to complete his notice period.

In respect of the alleged claims made to NHS diabetes specialist nurses by the three named Novo Nordisk employees about the complainant, the complainant had not provided details of the names of the nurses. In any event, two of the named employees had confirmed they did not make such claims. The third employee was no longer employed by Novo Nordisk.

The complainant was neither 'dismissed', nor did he 'resign' from Novo Nordisk as he was never an employee of Novo Nordisk.

It was Novo Nordisk's understanding, following a telephone conversation with the diabetes consultant that neither he/she nor his/her secretary had made a complaint about the complainant's behaviour to Novo Nordisk or its employees. Therefore there was no relevant correspondence Novo Nordisk could provide.

In respect of the context of the complainant's call(s) upon the diabetes consultant, Novo Nordisk understood this was in respect of his position discussing market access matters. Novo Nordisk did not have access to the complainant's employee personal record, as he had never been an employee of Novo Nordisk (he was an employee of the service provider).

Novo Nordisk stated that the investigation into this complaint had taken the form of interviewing/ speaking to those referred to within the letter and documenting this within signed statements. Signed statements from two of the three named Novo Nordisk employees were provided.

Pursuant to the above, Novo Nordisk was of the clear view that, aside from being baseless, these matters fell outside the scope of the Code. Novo Nordisk's view was that Clauses 8.2, 9.1 and 15.2 could not sensibly be applied to such a staff-related matter. In any event Novo Nordisk submitted that the complainant had provided no credible evidence to substantiate his allegations.

PANEL RULING

The Panel noted the clauses cited by the case preparation manager, Clauses 8.2, 9.1 and 15.2 of the Code. The 2014 Code came into operation on 1 January 2014 with a transition period for newly introduced requirements. The clauses cited in this case were the same in the 2014 and 2012 Second Edition (amended) Codes, thus the Panel used the 2014 Code.

The Panel noted that the complainant, who at the time of the complaint was an NHS associate director of commissioning, was formerly employed by a service provider working for Novo Nordisk in diabetes. The complainant stated that he had resigned from his position but had been advised by two specialist NHS nurses that three named Novo Nordisk employees had told them that he had been dismissed for specific reasons. These reasons included that a diabetes consultant and his secretary had each made a serious complaint about him. The Panel noted that both the complainant and Novo Nordisk agreed that neither the diabetes consultant nor his secretary had made such a complaint.

The Panel noted that the complaint related to comments made by the Novo Nordisk employees to two NHS diabetes nurse specialists. The Panel noted the scope of the Code as set out in Clause 1.2. It applied to the promotion of medicines for prescribing to health professionals and appropriate administrative staff and to certain non promotional activities.

The Panel noted that as the complaint concerned what was allegedly said externally to health professionals about the reasons why the complainant had left his position as an employee of a service provider working with Novo Nordisk including his conduct with other health professionals, it was a matter potentially covered by the Code.

The Panel noted that the complainant had to establish his case on the balance of probabilities. The complainant had not identified the nurses in question nor provided any evidence to demonstrate that the comments at issue had, in fact, been made to the nurses in question. The signed statements submitted by Novo Nordisk for two of the three named employees each denied that they had notified NHS diabetes nurses that the complainant had been dismissed. Neither statement referred to a complaint about his conduct or a breach of an SOP. The Panel, therefore, considered that the complainant had not met the burden of proof and ruled no breach of Clauses 8.2, 9.1 and 15.2 of the Code.

Complaint received **21 January 2014**

Case completed **1 May 2014**

CASE AUTH/2698/1/14

VOLUNTARY ADMISSION BY ASTELLAS

Declaration of sponsorship

Astellas Pharma voluntarily admitted that there was an error in the declaration of sponsorship on the front cover of a promotional item linked to the recent launch of Vesomni (tamsulosin HCl, solifenacin succinate). As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint the matter was taken up with Astellas.

Astellas explained that the Lower Urinary Tract Symptoms (LUTS) Consensus Statement was certified and the instruction to print given before comments in relation to pre-vetting had been received from the Medicines and Healthcare Products Regulatory Agency (MHRA). The MHRA subsequently requested that the acknowledgement of Astellas' involvement on the front page be expanded to explain that Astellas had been fully involved with the initiation, meeting organisation and author nomination for the consensus statement. Astellas tried to recall the item but it had already been distributed with the BMJ. Astellas submitted that it had not maintained high standards and acknowledged breaches of the Code.

The detailed response from Astellas is given below.

The Panel noted Astellas' submission that the MHRA requested that the declaration of sponsorship on the front page 'This edition is funded and has been checked for factual accuracy by Astellas Pharma Ltd' be changed to explain that Astellas had been fully involved with the initiation, meeting organisation and author nomination for the consensus statement. The Panel also noted the acknowledgements section on page 7 of the consensus statement read 'The consensus group meeting was organised and funded by Astellas Pharma Ltd. Editorial support was provided by a named communications agency and the final content was reviewed by Astellas Pharma Ltd'. The Panel was unsure of the role of the communications agency given the final statement on page 1 of the document was 'Medicine matters strives to bring you topical opinion from all clinical specialities. We also want to know what subjects matter to you. Email us at the [given communication agency's email address] with your suggestions'.

The Panel noted the Code required that care be taken with company sponsored reports of meetings and the like to ensure that they were not disguised promotion and that the declaration of sponsorship be sufficiently prominent to ensure that readers were aware of it at the outset. The wording of the declaration must be unambiguous so that readers would immediately understand the extent of the company's involvement and influence over the material. This was particularly important when companies were involved in the production of material which was circulated by an otherwise wholly independent party such as supplements to health journals'. In that regard the Panel noted that the item had been distributed as a supplement with the BMJ.

The Panel considered that the design of the front cover was such that the reader's eye was caught by the title, 'Medicine matters', the heading 'Optimal management of lower urinary tract symptoms (LUTS) in primary care: a consensus statement' and the subheading 'Consensus group members'. The declaration of sponsorship at the bottom of the left hand column on a light blue background was less prominent.

The fact that the consensus statement resulted from a meeting of eight health professionals that was organised and entirely funded by Astellas was not immediately clear at the outset. The Panel considered that the initial impression was that the 'consensus' was reached by an independent clinical authority, rather than an Astellas advisory board. The reference to prescribing information in small type font at the bottom of the front cover was not sufficiently prominent to dispel the initial impression. In the Panel's view the initial impression was compounded by the declaration of sponsorship in the bottom left hand column that 'This edition is funded and has been checked for factual accuracy by Astellas Pharma Ltd'; it implied that the consensus statement was independently produced material and that was not so. This was misleading and in the Panel's view amounted to disguised promotion. A breach of the Code was ruled.

The Panel considered that the declaration of sponsorship was misleading; it did not provide an unambiguous account of Astellas' involvement and misleadingly implied that the company had only funded a consensus statement written by a group of independent clinicians. A breach of the Code was ruled.

The Panel noted its comments above. In addition the Panel was extremely concerned that the material was certified and instruction given to print before the MHRA had provided its comments as part of the pre-vetting process. This was unacceptable. High standards had not been maintained and a breach of the Code was ruled as acknowledged by Astellas.

Astellas voluntarily admitted that there was an error in the declaration of sponsorship on the front cover of a promotional item, the Lower Urinary Tract Symptoms (LUTS) Consensus Statement. The item had already been the subject of a complaint from the Medicines and Healthcare Products Regulatory Agency (MHRA) which had requested that Astellas

print a corrective statement outlining its full involvement.

Astellas' product Vesomni (tamsulosin HCl, solifenacin succinate) was indicated for the treatment of moderate to severe storage symptoms and voiding symptoms associated with benign prostatic hyperplasia (BPH) in men who were not adequately responding to monotherapy.

The front page of the consensus statement bore the title 'Medicine matters' above the prominent heading 'Optimal management of lower urinary tract symptoms (LUTS) in primary care: a consensus statement'. Immediately beneath this was the subheading 'Consensus group members' in a highlighted dark blue box, followed by a list of clinicians who were consensus group members. The declaration of sponsorship appeared at the bottom of the left hand column and read 'This edition is funded and has been checked for factual accuracy by Astellas Pharma Ltd'. The statement 'Prescribing information for Betmiga (mirabegron) and Vesomni (solifenacin 6mg/tamsulosin 0.4mg) can be found on page 8 of this publication' appeared as a footnote to page 1. The acknowledgements on page 7 stated 'The consensus group meeting was organised and funded by Astellas Pharma Ltd. Editorial support was provided by a named communications agency and the final content was reviewed by Astellas Pharma Ltd'. Prescribing information for Vesomni and Betmiga appeared on the final page.

COMPLAINT

Astellas submitted that a cessation of vetting notice was issued to Astellas on 2 December 2013 with one outstanding item required for submission to the MHRA, the Lower Urinary Tract Symptoms (LUTS) Consensus Statement, which was submitted on 17 January 2014. Due to human error the item was certified on 13 January 2014 and the instruction to print the item given before any comments had been received from the MHRA. The MHRA had no objections to the actual consensus statement but in comments received on 22 January it requested that the acknowledgement of Astellas' involvement statement on the front page be expanded to explain that Astellas had been fully involved with the initiation, meeting organisation and author nomination for the consensus statement and not just an arm's length agreement which could have been inferred from the printed acknowledgement.

Until then Astellas had an excellent record with pre-vetting and no item had previously been certified before final comments had been received from the MHRA. However, on this occasion, perhaps due to the long gap between receiving the cessation notice and the item being ready for final approval with a holiday period in between, there was a breakdown in communication and a misunderstanding arose that the item was to be sent to the MHRA for reference purposes only (as sometimes is genuinely the case with cessation of vetting notices). However, the cessation of vetting notice clearly stated that the MHRA wished to see the consensus statement before it could be used.

Astellas tried to recall the item on 22 January but it had already been distributed with the BMJ and could not be recalled. Astellas had agreed to enclose a corrective statement with the BMJ on Saturday, 8 February in the form of a letter which had been agreed with the MHRA. Astellas would also individually contact anyone who had been handed a copy of the consensus statement and give them a copy of the corrective statement. The item was last used on 27 January. In addition, Astellas was reviewing its processes to ensure that this could not happen again and the individuals concerned had received additional training.

Astellas acknowledged a breach of Clauses 12.1 (disguised promotion) and 9.1 as clearly it had not maintained high standards in this case.

Astellas was asked to respond in relation to Clauses 9.1 and 9.10 of the 2014 Code.

RESPONSE

Astellas submitted that although Vesomni was not a black triangle product, Astellas was mindful of the possibility that a new combination product might be subject to pre-vetting and made contact with the MHRA in April 2013. The initial response was that the MHRA was not minded to vet advertising for Vesomni but might review the product in the future to consider whether vetting would be required. As the granting of a marketing authorization approached, Astellas sent a further email to the MHRA and it received a vetting invitation letter one week later.

Astellas had previously completed MHRA pre-vetting exercises for three newly launched products, Dificlir, Betmiga and Xtandi, during which a best working practice was established. Astellas provided copies of two separate presentations which had been developed and used by the medical information team and the Vesomni Brand team outlining the pre-vetting process and requirements. However, a formal standard operating procedure (SOP) had not been written or implemented describing this process.

Materials which were subject to MHRA pre-vetting review were usually handled by Astellas in the following way:

Medical information was the primary contact with the MHRA for the pre-vetting of materials. All correspondence was sent via the relevant medical information scientist covering the product within the department who also submitted materials for review. The progression of those submissions was documented on the materials tracking spreadsheet which was similarly maintained by the medical information scientist.

It was acknowledged that the MHRA expected that the material submitted for review should have undergone a full set of internal quality control and compliance checks and sign-off. Therefore, there had been an understanding that materials submitted to the MHRA for pre-vetting were required to have

reached the pre-certification stage. Materials were then sent by email to the MHRA assessor along with supporting references and a covering letter describing the purpose of the item. Once a response was received from the MHRA, it was circulated to the review team (marketing manager, product manager, medical adviser, medical information scientist) and further action undertaken incorporating any comments received.

This process was followed for all other materials that were submitted for Vesomni and resulted in a swift conclusion of MHRA pre-vetting. Astellas received a cessation of vetting letter dated 2 December 2013, with the stipulation that the output of the consensus group meeting would be submitted to the MHRA when available. A copy of this letter was circulated via email to the Vesomni review team. The piece was submitted to the MHRA on 17 January 2014. Due to human error, the item was certified on 13 January and the instruction to print the item given before the final piece was submitted to the MHRA and any subsequent comments received.

Astellas had until then an excellent record with pre-vetting and no item had previously been certified before final comments had been received from MHRA. Unfortunately, there was no mechanism in existence for retaining the material that was subject to MHRA pre-vetting within the electronic approval system whilst awaiting final comments and the release of the certified material was reliant upon human recall/tracking of the progress of these individual materials.

Clause 9.1

Astellas was committed to adhering to the MHRA pre-vetting process and had ensured implementation of all MHRA recommendations for all other materials associated with this product and for a number of other products which had previously been through the pre-vetting process. Astellas was aware of the possibility of pre-vetting early on and actively sought advice on this matter from the MHRA.

Once the error was identified, immediate remedial action was taken by Astellas. The MHRA was notified and agreed to the issue of the corrective statement in a letter circulated with the BMJ on 8 February. The MHRA also agreed with the actions proposed by Astellas to ensure the error was not repeated. Astellas self-reported the case to the PMCPA on the same day that agreement was reached with the MHRA.

Astellas acknowledged that the pre-vetting process should have been documented in a formal standard operating procedure (SOP). Its existing copy approval SOP would be updated to emphasise the importance of this process and a pre-vetting SOP was currently being formulated.

Astellas submitted that it took immediate action to further retrain the individuals directly involved and would also highlight the importance of the MHRA vetting process and the requirement to quarantine materials undergoing review by the MHRA in its next compliance training update meeting to all brand teams.

Astellas engaged Zinc Ahead to create an additional process stamp, 'Pending MHRA Approval', which would be uploaded (electronically) onto the original piece of material subject for review by the originator. This stamp was configured to electronically prevent those materials bearing the stamp to be uploaded to the certification stage of approval. Materials could only progress to certification once external written authority was received from the MHRA. This written authority must be scanned and added to the piece and a request made to the compliance manager or medical director via the Zinc helpdesk. The purpose was to reduce issues arising from human error or misunderstanding and informed all reviewers that the piece was currently under MHRA pre-vetting scrutiny.

The material tracking spreadsheet would be hosted on an internal shared drive enabling access for all members of the review team to check progression of the materials subject to pre-vetting.
Within the current copy approval process, medical information would also now be involved in an additional review cycle for MHRA pre-vetting materials.

Astellas submitted that it had remained committed to maintaining high standards throughout all of the steps and actions detailed above but acknowledged that this unfortunate incident may have, regrettably, resulted in a failure to demonstrate that.

Clause 9.10

Astellas reassured the Panel that this item was developed entirely in good faith following the format of the 'Medicine Matters' template. Many previously published supplements in this series, sponsored by other companies, had used a similar declaration where their level of support and involvement had been comparable. There was no intention to mislead the readership as to the involvement of Astellas in the development of the document, and despite the additional disclosure of the nature and extent of its involvement in the acknowledgements section at the end of the material, Astellas recognised that the wording of the declaration on the front cover, which it believed to have been 'sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset', may not have been sufficiently 'unambiguous such that the readers would have immediately understood the extent of the company's involvement and influence over the material'.

Clause 12.1

In response to a request by the Panel for comment on Clause 12.1, Astellas submitted that Clause 12.1 simply stated that 'Promotional material and activities must not be disguised'. The supplementary information went on to state that 'promotional material in journals must not resemble independent

editorial matter'. In a recent case (AUTH/2610/6/13) the company was found in breach of Clause 12.1 by having promotional material closely resembling the main journal house style and in another recent case (AUTH/2622/7/13) a representative's email was not explicit enough about the nature of an invitation to a promotional webcast and there was no prescribing information attached to the email. Astellas had a clear declaration of funding on the front cover of the LUTS consensus statement (albeit not as complete as it would have wished), an acknowledgement at the end of the article which also mentioned funding the actual meeting where the consensus statement was agreed and there was prescribing information on the last page indicating that this was clearly a promotional piece. Astellas submitted that there was certainly no attempt to disguise the consensus statement and make it appear as anything other than a promotional item. Astellas submitted that it was also worth noting that the MHRA found the consensus statement to be balanced as it had no issues with the content, just the declaration on the front cover. It was therefore hard to know if a breach of Clause 12.1 did occur on this narrow point of interpretation of the word 'disguise'. Astellas however as previously stated accepted that on this occasion high standards had not been maintained and acknowledged a breach of Clause 9.1.

PANEL RULING

The Panel noted that Astellas and the case preparation manager referred to a number of clauses of the 2014 Code. This came into operation on 1 January 2014 with a transition period for newly introduced requirements. The clauses cited, 9.1, 9.10 and 12.1, were the same in the 2014 and Second 2012 Edition (amended) Codes, thus the Panel used the 2014 Code.

The Panel noted Astellas' submission that the MHRA requested that the declaration of sponsorship on the front page 'This edition is funded and has been checked for factual accuracy by Astellas Pharma Ltd' be changed to explain that Astellas had been fully involved with the initiation, meeting organisation and author nomination for the consensus statement. The Panel also noted the acknowledgements section on page 7 of the consensus statement read 'The consensus group meeting was organised and funded by Astellas Pharma Ltd. Editorial support was provided by a named communications agency and the final content was reviewed by Astellas Pharma Ltd'. The Panel was unsure of the role of the named communications agency given the final statement on page 1 of the document was 'Medicine matters strives to bring you topical opinion from all clinical specialities. We also want to know what subjects matter to you. Email us at [the given communication agency's email address] with your suggestions'.

The Panel noted the supplementary information to Clause 12.1 Disguised Promotional Material stated, *inter alia*, that 'Care must be taken with company sponsored reports of meetings and the like to ensure that they are not disguised promotion. Sponsorship must be declared in accordance with Clause 9.10'. The supplementary information to Clause 9.10, Declaration of Sponsorship stated that 'the declaration of sponsorship must be sufficiently prominent to ensure that readers are aware of it at the outset. The wording of the declaration must be unambiguous so that readers will immediately understand the extent of the company's involvement and influence over the material. This is particularly important when companies are involved in the production of material which is circulated by an otherwise wholly independent party such as supplements to health journals'. In this regard the Panel noted that the item had been distributed as a supplement with the BMJ.

The Panel considered that the design of the front cover was such that the reader's eye was caught by the title, 'Medicine matters', the heading 'Optimal management of lower urinary tract symptoms (LUTS) in primary care: a consensus statement' and the subheading 'Consensus group members'. The declaration of sponsorship at the bottom of the left hand column on a light blue background was less prominent.

The fact that the consensus statement resulted from a meeting of eight health professionals that was organised and entirely funded by Astellas was not immediately clear at the outset. The Panel considered that the initial impression created by the heading and the overall design of the page was that the 'consensus' was reached by an independent clinical authority, rather than an Astellas advisory board. The reference to prescribing information in small type font at the bottom of the front cover was not sufficiently prominent to dispel the initial impression. In the Panel's view the initial impression was compounded by the declaration of sponsorship in the bottom left hand column that 'This edition is funded and has been checked for factual accuracy by Astellas Pharma Ltd'; it implied that the consensus statement was independently produced material and that was not so. This was misleading and in the Panel's view amounted to disguised promotion. A breach of Clause 12.1 was ruled.

The Panel considered that the declaration of sponsorship was misleading; it did not provide an unambiguous account of Astellas' involvement and misleadingly implied that the company had only funded a consensus statement written by a group of independent clinicians. A breach of Clause 9.10 was ruled.

The Panel noted its comments above. In addition the Panel was extremely concerned that the material was certified and instruction given to print before the MHRA had provided its comments as part of the pre-vetting process. This was unacceptable. High standards had not been maintained and a breach of Clause 9.1 was ruled as acknowledged by Astellas.

During its consideration of this case the Panel noted Astellas' submission that the MHRA had 'no objection to the actual consensus statement …'. The Panel noted that this was not so. The MHRA stated in a letter dated 22 January that it had not

carried out a detailed review of the consensus statement itself but would not object in principle to this material. The accuracy of the statistics, disease and background information were Astellas' responsibility. The Panel considered that the company's submission on this point was misleading and not a fair reflection of the MHRA's position as stated in its letter dated 22 January. It was essential that the Authority was able to rely on the accuracy of a company's submission. The Panel requested that the company be advised of its views.

Complaint received **30 January 2014**

Case completed **16 April 2014**

ANONYMOUS GP v GLAXOSMITHKLINE

Relvar advertisements

An anonymous, contactable general practitioner complained about two bullet points in journal advertisements for Relvar Ellipta (fluticasone furoate and vilanterol inhalation powder) placed by GlaxoSmithKline UK Ltd. One of the advertisements was about the use of Relvar in asthma and the other was about its use in chronic obstructive pulmonary disease (COPD). The two claims at issue appeared in both advertisements.

With regard to the claim 'Delivered in a straightforward device' the complainant did not see why undue emphasis was put on an inhaler feature that worked in exactly the same way as existing inhalers that could be prescribed; it really seemed no different to the Symbicort Tubohaler. The complainant also referred to the claim 'That offers value to the NHS' and noted that the advertisements did not explain why or how Relvar offered value.

The detailed response from GlaxoSmithKline is given below.

The Panel noted GlaxoSmithKline's submission that the claim 'Delivered in a straightforward device' was a stand-alone claim which did not refer to any other inhalation device in asthma or COPD and thus did not invite any comparisons with them. The claim was referenced to Riley *et al* in the COPD advertisement. The study showed that following initial instruction, 98% (n=618/632) of COPD patients used Ellipta correctly at day 1. At 6 weeks without further verbal instruction or demonstration, 99% of subjects still used their Ellipta inhaler correctly and rated it either very easy or easy to use.

The claim in the asthma advertisement was referenced to Svedsater *et al* (2013a). The results of that study found that 95% of patients used the Ellipta device correctly at the baseline visit (as adjudicated by an investigator) after a single demonstration of correct usage (n=1,049). At week 2 and 4, >99% of patients used the inhaler correctly and 94% found the Ellipta device was easy or very easy to use.

The Panel noted that the steps for Relvar Ellipta on the product website, as derived from the package information leaflet (PIL), showed that sliding the cover open until a click was heard primed the device for inhalation. The Panel noted GlaxoSmithKline's submission that unlike Symbicort Turbohaler, no additional loading step was required. In addition the dose counter of the Ellipta device counted down by one for each dose administered unlike the dose counter on the Turbohaler which was only marked in intervals of 10.

The Panel considered that, given the details regarding the steps on how to use the Relvar device on the product website and in the PIL and the data from Riley *et al* and Svedsater *et al* (2013a), the claim 'Delivered in a straightforward device' was not misleading and unsubstantiable as alleged. No breach of the Code was ruled.

With regard to the claim 'That offers value to the NHS' and the complainant's concern that there was no explanation as to why or how Relvar offered value, the Panel noted that promotional material did not need to contain all of the relevant information to substantiate a claim. All claims had to be capable of substantiation and such substantiation had to be provided on request. The Panel noted that GlaxoSmithKline had provided information showing how Relvar Ellipta might offer value to the NHS including its effective once daily dosage regimen and ease of use of the device and the presumed effect this would have on compliance. The Panel further noted that, from information provided by GlaxoSmithKline, the two Relvar Ellipta preparations (92/22mcg) and (184/22mcg) were the least expensive options in the mid and high dose inhaled corticosteroid/long-acting beta2-agonist dosage bands for asthma. Only the 92/22mcg dose was licensed in COPD and was less expensive than Seretide 500/50mcg Accuhaler and Symbicort Turbohaler 400/12mcg or 200/6mcg.

The Panel noted that the claim 'That offers value to the NHS' was non-specific and did not make it clear exactly what value the device would offer the NHS. The Panel, however, noted the detailed information provided by GlaxoSmithKline and did not consider that, whether considered in monetary or non monetary terms, the claim was misleading or unsubstantiable. No breach of the Code was ruled.

The Panel noted its rulings above and consequently ruled no breach of the Code as it did not consider that GlaxoSmithKline had failed to maintain high standards.

An anonymous, contactable general practitioner complained about advertisements (refs UK/FFT/0096l/13 and UK/FFT/0056/13) for Relvar Ellipta (fluticasone furoate and vilanterol inhalation powder) placed in the 5 February issue of Prescriber and the 8 February issue of the BMJ by GlaxoSmithKline UK Ltd.

Relvar Ellipta was indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta2-agonists and for the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD) with a FEV1 < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

The advertisements related either to the use of Relvar in COPD (ref UK/FFT/0096l/13) or in asthma (ref UK/FFT/0056/13). Each advertisement contained four bullet points the first three of which were common to both.

COMPLAINT

The complainant referred to two bullet points which appeared in both advertisements. With regard to the claim 'Delivered in a straightforward device' the complainant stated that in his/her view, having looked at the product website and the inhaler demonstration, the device steps were really no different to Symbicort Turbohaler where one primed the device and inhaled. The complainant did not see why undue emphasis was put on an inhaler feature that worked in exactly the same way as existing inhalers that could be prescribed. The complainant also referred to the claim 'That offers value to the NHS' and noted that the advertisements did not explain why or how Relvar offered value.

GlaxoSmithKline was asked to respond in relation to Clauses 7.2, 7.4 and 9.1 of the Code.

RESPONSE

GlaxoSmithKline stated that Relvar Ellipta was a new inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) combination product, which was licensed in the UK for both asthma and COPD as follows:

- The regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta2-agonist and inhaled corticosteroid) was appropriate ie in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta2-agonists.

- The symptomatic treatment of adults with COPD with a FEV1 < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

Two doses were licensed in asthma, 92/22mcg and 184/22mcg; only the 92/22mcg dose was licensed in COPD.

The advertisements informed health professionals about the availability of this new medicine and very briefly highlighted a few of its key attributes by means of four bullet points. Obviously, these four claims, as well as several others, which showed the total value that Relvar could offer the NHS were expanded upon in much greater depth in other materials specifically designed for health professionals and appropriate administrative staff for example the detail aid, formulary pack and budget impact model. Additionally, health professionals and appropriate administrative staff could also discuss, in detail, clinical data and the potential budgetary impact of using Relvar with GlaxoSmithKline employees such as representatives and health outcome consultants.

'Delivered in a straightforward device'

GlaxoSmithKline stated that this was a simple, stand-alone claim. It did not refer to any other inhalation device in asthma or COPD and as such did not invite any comparisons with them. The claim related to the Ellipta inhalation delivery device which was the only device via which patients could receive Relvar. Currently the Ellipta device was only available for Relvar.

The claim was substantiated in the COPD advertisement by the reference to Riley *et al* (2013). One of the objectives of this study was to determine whether COPD patients could easily use the Ellipta device. Following initial instruction 98% of patients (n=618/632) used Ellipta correctly at day one. Correct Ellipta inhaler use was re-assessed after 6 weeks, without further verbal instruction or demonstration to the patient; 99% (n=580/587) of subjects still used their Ellipta correctly. After 6 weeks of treatment; 99% (580/587) of patients rated the Ellipta inhaler as either very easy or easy to use.

The claim was substantiated in the asthma advertisement by the reference to Svedsater *et al* (2013a). The objective of this study was to assess participating patients' competence in the use of the Ellipta device, as judged by trial investigators. Participants were involved in one of three clinical studies which were part of the Relvar asthma development programme. Trial investigators assessed patients' competence using the Ellipta device at baseline, and again at weeks 2 and 4 of the treatment period. Patients were also asked to complete an ease of use questionnaire; one of the questions required rating the inhaler as very easy, easy, neutral, difficult, or very difficult to use.

The study results showed that 95% of patients used the Ellipta device correctly at the baseline visit (as adjudicated by the investigator) after a single demonstration of correct usage (n=1,049). Furthermore, when inhaler technique was reassessed at weeks 2 (n=1,024) and 4 (n=988) >99% of patients used the inhaler correctly. Additionally 94% (929/989) of patients reported the Ellipta device to be easy or very easy to use.

Although not referenced in the advertisements, Svedsater *et al* (2013b) conducted one-on-one interviews with asthma and COPD patients who had completed studies involving the Ellipta device, to find out what they thought of it. Several participants spontaneously reported that the device was straightforward and intuitive to use.

GlaxoSmithKline submitted that the above evidence, involving both asthma and COPD patients, strongly supported the claim that the Ellipta device was a straightforward device.

GlaxoSmithKline noted the complainant's allegation that undue emphasis was placed on the inhaler device by stating that it was a straightforward device. GlaxoSmithKline submitted that in asthma and COPD, consideration of the inhalation device was an important part of the prescribing decision for a new medicine. Inhalers, although commonly used in asthma and COPD, were often used suboptimally

which led to uncontrolled disease and increased costs, either as a result of uncontrolled disease or increased use of relief medication or preventative therapy (Price *et al*, 2013, Press *et al*, 2011). Price *et al* highlighted that one of the major compliance issues for asthma patients using inhalers was unintentional non-compliance ie when a patient made inadvertent mistakes using the device. They concluded that the more complex an instruction and the more handling steps needed to start the inhalation process, the greater the chance of an error occurring. In fact, they suggested that one way in which a device could be simplified was by combining the activation of the device with another step such as removing the cap. This was a feature of the Ellipta device.

For these reasons, GlaxoSmithKline submitted that it was important to tell clinicians that asthma and COPD patients found that the Ellipta device was straightforward; a claim substantiated by Riley *et al* and Svedsater *et al* (2013a).

Although this was a stand-alone claim, based on Ellipta device data only, the anonymous complainant compared information on the product website to his/her impression about the use of the Symbicort Turbohaler and stated that the device steps were really no different to Symbicort Turbohaler and an inhaler feature that worked in exactly the same way as existing inhalers. Given the nature of the stand-alone claim at issue, GlaxoSmithKline submitted that it was not appropriate to compare, in this response, how the Ellipta device worked with all the other available inhalers. However, given that the Symbicort Turbohaler was specifically mentioned, GlaxoSmithKline noted that the steps required to use the two inhalers were different.

The package information leaflet (PIL) for Symbicort Turbohaler involved a 5 stage approach for first 'Preparing your new Symbicort Turbohaler' followed by 9 steps for 'How to take an inhalation'. GlaxoSmithKline noted that in addition to removing the cover, the Turbohaler had to be loaded each time before use by turning the red grip at the base of the inhaler in two separate directions. The steps for Relvar Ellipta shown on the product website (which were derived from the Relvar Ellipta PIL) showed that with the Ellipta inhaler, opening the cover was all that was required to prepare the device for inhalation. Unlike the Turbohaler, no additional loading step was required. GlaxoSmithKline also noted that there were only four steps within the instructions for the Ellipta device in the PIL. Also, the dose counter on the Turbohaler was only marked in intervals of 10, therefore it did not show every dose. In particular, patients needed to know how many doses remained once the counter reached 10, so as to ensure they did not reach 0 without having a replacement inhaler. With the Ellipta device the dose counter counted down by 1 for each dose administered.

In summary, GlaxoSmithKline submitted that in both asthma and COPD the claim 'Delivered in a straightforward device' was accurate, fair, balanced and objective and capable of substantiation. The claim was therefore not in breach of Clauses 7.2 and 7.4 of the Code.

'That offers value to the NHS'

This claim was not referenced in the advertisements. However, in keeping with Clauses 7.4 and 7.5, GlaxoSmithKline could provide substantiation for the claim to any health professional or appropriate administrative staff who requested it.

GlaxoSmithKline submitted that the introduction of a new medicine and the value it could bring to the NHS might be considered both in monetary and non monetary terms. When clinicians, commissioning bodies and health appraisal organisations such as the National Institute for Health and Care Excellence (NICE) reviewed the value of a new medicine, they not only looked at the cost of the medicine but also assessed clinical efficacy, safety and other factors such as the route of administration, dosing regimen and service charges. Henshall *et al* (2013) reported that the Health Technology Assessment International Policy Forum concluded that in addition to elements related to cost, value also incorporated measures related to patient benefits such as clinical outcomes.

1 Non monetary value

GlaxoSmithKline noted that Relvar Ellipta was a new ICS/LABA treatment option for COPD and asthma and the first once daily ICS/LABA for COPD and asthma, which produced clinically significant outcomes. Despite the availability of a number of different treatments there still remained a large burden of illness with COPD and asthma in the UK.

It was estimated that three million people in England had COPD, with only just under a million diagnosed as such. COPD was the second most common cause of emergency admission to hospital; around a third of those admitted to hospital were readmitted within a month of discharge. COPD caused around 23,000 deaths in England each year. The total annual cost of COPD to the NHS was over £800 million (NHS Medical Directorate COPD Commissioning Toolkit, 2012).

The prevalence of asthma in England was among the highest in the world. In the UK, 5.4 million people currently received treatment for asthma. There were around 1,000 deaths from asthma a year in the UK, the majority of which were preventable. Most admissions were emergencies and 70% might have been prevented with appropriate early interventions; asthma cost the NHS an estimated £1 billion a year. Many people with asthma did not achieve freedom from symptoms and a recent large scale survey reported that around 35% of adult asthmatics had had an asthma attack in the previous 12 months (NICE Quality standard for asthma, 2013; An outcomes strategy for COPD and Asthma, Department of Health Best Practice Guidance, 2012).

The place of ICS/LABAs was well recognised within treatment guidelines such as the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guideline on the management of asthma

(revised 2011) and the NICE clinical guideline: Management of COPD in adults in primary and secondary care, June 2010. Although a number of ICS/LABAs were already licensed in COPD and asthma, Relvar was the first ICS/LABA combination that was licensed for once daily use only, due to its ability to provide continuous 24 hour efficacy from a once daily dose. GlaxoSmithKline submitted that due to the features highlighted below, the introduction of Relvar was of value to the NHS.

2 Once daily vs twice daily

COPD

GlaxoSmithKline submitted that the availability of a once daily ICS/LABA maintenance treatment in COPD was a valuable addition to the NHS. Patient adherence to COPD treatment was generally low and suboptimal (Charles *et al*, 2010). The importance of improved compliance was highlighted by the finding that <80% adherence to twice daily Seretide 500/50mcg was linked to increased hospital admissions and death (Vestbo *et al*, 2009). There was some evidence that a once daily COPD inhaler therapy might improve compliance (in the long-acting muscarinic antagonist (LAMA) class). In a retrospective analysis of 50,076 patients in the US looking specifically at adherence (Toy *et al*, 2011), COPD patients initiated on once daily tiotropium (n=3,678) had significantly higher adherence over 12 months than patients initiated twice a day Seretide 500/50mcg and Symbicort 400/12mcg (n=25,011) (43.3% vs 37% respectively, p<0.0001).

Currently there was no direct evidence that Relvar 92/22mcg improved patient compliance vs ICS/LABA combinations dosed twice daily. As might be expected in the controlled environment of a randomised control trial, in the head-to-head study between Relvar 92/22mcg and Seretide 500/50mcg (Agusti *et al*, 2013) compliance rates were very high in both treatment arms (97.5%). It was not unreasonable to postulate that in the real world setting, compliance rates might be less and that a once daily regime might result in improved compliance rates vs a twice daily regime.

Finally, with an increasing number of COPD patients taking 'triple therapy' (concomitant ICS/LABA and LAMA preparations), a once daily ICS/LABA would complement the once daily dosing schedule of the most widely prescribed LAMAs (Spiriva and Seebri).

Asthma

GlaxoSmithKline submitted that the availability of a once daily ICS/LABA maintenance treatment in asthma was a valuable addition to the NHS, as non-adherence to maintenance therapies was common and might contribute to poor asthma control (Haughney *et al*, 2008). As stated above, there was no direct evidence that Relvar improved patient compliance vs ICS/LABA combinations dosed twice daily. As might be expected in the controlled environment of a randomised control trial, in the head-to-head study between Relvar 92/22mcg and Seretide 250/50mcg (Woodcock *et al*, 2013) compliance rates were very high in both treatment arms (>94%). However, once again it was not unreasonable to postulate that in the real world setting, compliance rates might be less and that a once daily regimen might result in improved compliance rates vs a twice daily regimen. Indeed, it had been demonstrated that compliance with a once daily regimen was greater than with a twice daily regimen; in a 12-week study (Price *et al*, 2010) designed to mimic an actual clinical setting in subjects with mild to moderate persistent asthma, compliance with once daily mometasone was significantly better than with twice daily mometasone.

For a number of reasons (eg forgetfulness, busy lifestyle, reliance on a carer), some COPD and asthma patients might find taking a medicine only once a day a better treatment option and Relvar offered these patients the opportunity to manage their condition with only a single daily dose, something not offered by other currently available ICS/LABAs.

3 Efficacy

GlaxoSmithKline stated that the clinical development programme for Relvar in COPD and asthma looked at a number of endpoints which were clinically important for patients and health professionals. Two important endpoints should be considered.

a) COPD

Lung function: Forced Expiratory Volume in 1 second (FEV1)

GlaxoSmithKline submitted that FEV1 was the most extensively used and one of the most repeatable lung function parameters to measure the obstructive element of COPD and to determine treatment strategies (EMA, 2012). In a 12 week head-to-head study, once daily Relvar 92/22mcg demonstrated an improvement from baseline trough of 0-24hr weighted mean FEV1 of 130mL compared with Seretide 500/50mcg twice daily which increased weighted mean FEV1 by 108mL (Agusti *et al*). The difference between the treatment groups of 22mL was not statistically significant (p=0.282); this study was a superiority study and as such the primary endpoint was not met. However, a clinically meaningful increase of FEV1 was accepted to be 100mL (NICE 2010 COPD clinical guidelines) and as such both Relvar and Seretide achieved this clinically meaningful increase from baseline.

This data demonstrated how clinically meaningful improvements in lung function were now possible with a once daily ICS/LABA.

COPD exacerbations

Exacerbations were possibly the most impactful consequence of COPD for both the patient and the local health economy. NICE described exacerbations as 'important events for patients and the NHS. Patients experiencing frequent exacerbations have a worse prognosis and much of the cost of caring

for COPD results from managing exacerbations. Strategies to reduce the frequency and impact of exacerbations are essential'.

In two one year studies (Dransfield *et al*, 2013), the annual rate of moderate/severe exacerbations was compared between Relvar 92/22mcg once daily and the LABA component alone, vilanterol 22mcg once daily. In the pooled analysis of these two studies, Relvar patients had a yearly rate of moderate and severe exacerbations of 0.81, compared with a rate of 1.11 for patients on vilanterol 22mcg alone. This represented a relative reduction in the yearly rate of moderate and severe exacerbations of 27%. Although direct comparisons of exacerbation reduction rates between studies was difficult due to different definitions of exacerbation and different baseline patient characteristics, the reduction seen in these studies were consistent with those seen for other licensed ICS/LABAs (Dransfield *et al*). This data demonstrated how clinically meaningful reductions in COPD exacerbations were now possible with a once daily ICS/LABA.

b) Asthma

Lung function: Forced Expiratory Volume in 1 second (FEV1)

GlaxoSmithKline submitted that FEV1 reflected asthma severity and correlated with symptoms and healthcare utilisation. It was well validated, reproducible, and an important element which defined asthma control. Relvar 92/22mcg given once daily was compared with Seretide 250/50mcg given twice daily in a 24 week head-to-head study (Woodcock *et al*). Clinically meaningful improvements from baseline in 0-24h weighted mean FEV1 were seen with both Relvar (341mL) and Seretide (377mL); although it should be noted that the primary endpoint of superiority was not met as the difference between the two treatment arms was not statistically significant (-37mL; p= 0.162).

This data demonstrated how clinically meaningful improvements in lung function were now possible with a once daily ICS/LABA.

Asthma exacerbations

GlaxoSmithKline submitted that prevention of asthma exacerbations was widely recognised as an important component of establishing ideal asthma control. It could be argued that exacerbations constituted the greatest risk to patients, caused anxiety to patients and their families, resulted in the greatest stress on healthcare providers, and generated the greatest cost to the healthcare system. The time to first severe exacerbation and annualised rate of severe exacerbations was compared for Relvar 92/22mcg vs fluticasone furoate 92mcg alone (Bateman *et al*, 2013). Relvar significantly delayed the time to first severe asthma exacerbation relative to fluticasone furoate. The adjusted probability of experiencing a severe asthma exacerbation by 52 weeks was 15.9% in the fluticasone group and 12.8% in the Relvar group. The hazard ratio for Relvar 92/22mcg vs fluticasone furoate 92mcg was 0.795 representing a 20% risk reduction. The rate of severe asthma exacerbations per patient per year was significantly lower in the Relvar 92/22mcg group than in the fluticasone furoate 92mcg group (0.14 vs 0.19), a reduction in rate of 25%. These results were consistent with the results of other studies which demonstrated the benefit of adding a LABA to an ICS in reducing the risk of severe asthma exacerbations (Bateman *et al*).

This data demonstrated how clinically meaningful reductions in asthma exacerbations were now possible with a once daily ICS/LABA.

Safety

GlaxoSmithKline submitted that in its separate clinical development programmes, 6,237 COPD patients and 7,034 asthmatics were included in integrated assessments of adverse reactions. Relvar was generally well tolerated; the range and frequency of adverse events seen was consistent with twice daily ICS/LABAs available for the treatment of asthma and COPD. GlaxoSmithKline noted that the risk of pneumonia in COPD patients was similar to that reported within the summaries of product characteristics (SPCs) of other ICS/LABAs licensed for COPD.

Device

GlaxoSmithKline reiterated that data showed that the Ellipta device was straightforward to use. This was important as clinicians needed to be confident that patients would find their inhaler easy to use and thus be able to benefit fully from the treatment. In addition to the introduction of a new medicine for COPD and asthma, GlaxoSmithKline submitted that the introduction of a new straightforward to use device also meant that Relvar Ellipta offered value to the NHS.

In summary GlaxoSmithKline submitted that the efficacy and safety profile seen with Relvar, coupled with the straightforward Ellipta device, meant that Relvar brought clinically meaningful benefits to COPD and asthma patients within the NHS. Moreover, such benefits, which were comparable to those seen with other ICS/LABAs, could be achieved for the first time with once daily dosing.

4 Monetary value

GlaxoSmithKline submitted that NHS clinicians and payors might expect that as the first ICS/LABA with only once daily dosing, Relvar would be priced at a premium. However, the two preparations of Relvar Ellipta were £27.80 (92/22mcg) and £38.87 (184/22mcg) for 30 days. These prices meant that the two Relvar preparations were the cheapest in 2 of the 3 steroid based dosage strengths for ICS/LABAs in asthma, ie mid dose and high dose (MIMS Feb 2014). Prescription data (Cegedim Patient Data Report, 2013) showed that over 50% of new ICS/LABA patients stepped up from an ICS alone, fell within the mid and high dose categories. Therefore,

if a clinician wished to prescribe Relvar to such patients instead of other available ICS/LABAs, this would result in cost savings in a significant number of asthma patients treated within the NHS. Only the 92/22mcg dose of Relvar Ellipta (£27.80) was licensed in COPD. This was the cheapest ICS/LABA licensed for COPD (30 day cost: Seretide 500/50mcg Accuhaler, £40.92; Symbicort Turbohaler 400/12mcg or 200/6mcg, £38.00) and again highlighted the monetary value afforded to health professionals who prescribed Relvar Ellipta instead of other ICS/LABAs (MIMS Feb 2014). In conclusion, for the first time Relvar Ellipta provided clinicians and patients with an ICS/LABA (a major class of medicine in the treatment of COPD and asthma) which delivered continuous 24 hour efficacy from a once daily dose. Furthermore, the device had been shown to be straightforward for patients to use. Relvar Ellipta was also priced such that it was the cheapest treatment option for patients who required a mid or high dose of ICS within an ICS/LABA combination in asthma, and was also the cheapest ICS/LABA for COPD. Thus the statement that 'Relvar offers value to the NHS' was accurate, fair, balanced and objective and capable of substantiation in COPD and asthma. GlaxoSmithKline refuted any breach of Clauses 7.2 and 7.4.

Finally, in the absence of the above breaches, GlaxoSmithKline refuted any breach of Clause 9.1 as it maintained that high standards had been maintained in the two advertisements. GlaxoSmithKline's internal processes required that all promotional claims were capable of substantiation prior to certification; this was achieved through the requirement for commercial and medical signatories to discuss such claims in a formal review meeting, and for material to be reviewed with references before final certification.

PANEL RULING

The Panel noted the clauses cited by the case preparation manager, Clauses 7.2, 7.4 and 9.1 of the Code. The 2014 Code came into operation on 1 January 2014 with a transition period for newly introduced requirements. The clauses cited in this case were the same in the 2014 and 2012 Second Edition (amended) Codes, thus the Panel used the 2014 Code.

The Panel noted the complainant's concern regarding the claims 'Delivered in a straightforward device' and 'That offers value to the NHS' which appeared as bullet points in both Relvar advertisements. The Panel noted GlaxoSmithKline's submission that the purpose of the Relvar advertisements was to make health professionals aware of the availability of the new medicine and to very briefly highlight a few of its key attributes by means of four bullet points.

The complainant alleged that looking at the product website and the inhaler demonstration, the device steps were no different to Symbicort Turbohaler where one primed the device and inhaled. The Panel noted GlaxoSmithKline's submission that the statement was a stand-alone claim which did not refer to any other inhalation device in asthma or COPD and thus did not invite any comparisons with them.

The Panel noted that the claim 'Delivered in a straightforward device' was referenced to Riley *et al* in the Relvar COPD advertisement. The study showed following initial instruction, 98% (n=618/632) of COPD patients used Ellipta correctly at day 1. At a 6 week re-assessment without further verbal instruction or demonstration, 99% (n=580/587) of subjects still used their Ellipta inhaler correctly. After 6 weeks of treatment, 99% (580/587) of patients rated the Ellipta inhaler as either very easy or easy to use.

The claim in the Relvar asthma advertisement was referenced to Svedsater *et al* (2013a). The objective of this study was to assess participating patients' competence in the use of the Ellipta device, as judged by trial investigators. Participants were involved in one of three clinical studies which were part of the Relvar asthma development programme. The results of the study found that 95% of patients used the Ellipta device correctly at the baseline visit (as adjudicated by the investigator) after a single demonstration of correct usage (n=1,049). At weeks 2 (n=1,024) and 4 (n=988) >99% of patients were using the inhaler correctly and 94% (929/989) of patients reported the Ellipta device to be easy or very easy to use.

The Panel noted that the steps for Relvar Ellipta on the product website, as derived from the package information leaflet (PIL), showed that sliding the cover open until a click was heard primed the device for inhalation. The Panel noted GlaxoSmithKline's submission that unlike Symbicort Turbohaler, no additional loading step was required. In addition the dose counter of the Ellipta device counted down by one for each dose administered unlike the dose counter on the Turbohaler which was only marked in intervals of 10.

The Panel considered that, given the details regarding the steps on how to use the Relvar device on the product website and in the PIL and the data from Riley *et al* and Svedsater *et al* (2013a), the claim 'Delivered in a straightforward device' was not misleading and unsubstantiable as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted with regard to the claim 'That offers value to the NHS', the complainant's concern that the advertisements did not explain why or how Relvar offered value.

The Panel noted promotional material did not need to contain all of the relevant information to substantiate a claim, however all claims had to be capable of substantiation and such substantiation had to be provided on request. The Panel noted that GlaxoSmithKline had provided information showing how Relvar Ellipta might offer value to the NHS including its effective once daily dosage regimen and ease of use of the device and the presumed

effect this would have on compliance. The Panel further noted that, from information provided by GlaxoSmithKline, the two Relvar Ellipta preparations (92/22mcg) and (184/22mcg) were the least expensive options in the mid and high dose ICS/LABA dosage bands for asthma. Only the 92/22mcg dose was licensed in COPD and was less expensive than Seretide 500/50mcg Accuhaler and Symbicort Turbohaler 400/12mcg or 200/6mcg.

The Panel noted that the claim 'That offers value to the NHS' was non-specific and did not make it clear exactly what value the device would offer the NHS. The Panel, however, noted the detailed information provided by GlaxoSmithKline and did not consider that, whether considered in monetary or non monetary terms, the claim was misleading or unsubstantiable. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted its rulings above and consequently ruled no breach of Clause 9.1 as it did not consider that GlaxoSmithKline had failed to maintain high standards.

Complaint received **11 February 2014**

Case completed **25 April 2014**

ANONYMOUS v CHUGAI

Conduct of a representative

An anonymous, non-contactable haematologist from a district general hospital complained that pharmaceutical company representatives encouraged the use of medicines by referencing inaccurate information. The complainant referred in particular to a recent meeting with a Chugai representative who had promoted Granocyte (lenograstim).

The complainant had a number of concerns including that the representative had shown information that was of no benefit to the complainant and wasted both of their time; the information included data showing a recommendation from a European transplant group which was not a stipulation and that the representative had suggested that data from healthy donors could be extrapolated to fit neutropenia patients who were normally ill with cancer.

The complainant also alleged that the representative had told a senior nurse that the commissioning of Granocyte now came direct from the new NHS commissioning board. The complainant was concerned that the representatives had been given incorrect information by Chugai.

The detailed response from Chugai is given below.

The Panel noted that extreme dissatisfaction was usually required on the part of an individual before he/she was moved to complain. The Panel considered that Chugai was in a difficult position given that the complainant was anonymous and had not identified a hospital or a geographical location or named the representative. The Panel noted that Chugai had interviewed the representatives and provided copies of, *inter alia*, the Granocyte e-sales aid, and the relevant briefing document. Conversely, the complainant, who had the burden of proving his/her complaint on the balance of probabilities, had not provided any material to support his/her allegations. As the complainant was non-contactable, it was not possible to obtain more information from him/her. A judgement had to be made on the evidence provided by the parties.

The Panel noted the allegation that the representative had wrongly suggested that data from healthy donors could be extrapolated to neutropenic patients. Chugai agreed that such extrapolation was neither ethical nor correct. The Panel noted that neither the e-sales aid nor the briefing document implied that such extrapolation was possible. In that regard the Panel did not consider that the briefing material advocated a course of action which would be likely to lead to a breach of the Code and no breach was ruled. Bearing in mind the materials used by the representatives, the Panel considered that the complainant had not demonstrated that the representative had claimed that data from healthy donors could be extrapolated to neutropenic patients. No breach was ruled.

The Panel noted Chugai's submission that although the use of Granocyte to mobilise stem cells in patients and donors was more likely in tertiary units, subsequent care was typically managed at the district general hospital. In the Panel's view it was thus not unreasonable that haematologists in secondary care might be informed about the use of Granocyte in tertiary units. In that regard, based on the material before it, the Panel did not consider that the representative in question had failed to maintain a high standard of ethical conduct by wasting the complainant's time as alleged. No breach of the Code was ruled.

The Panel noted that the e-sales aid contained the statement 'The use of biosimilar [granulocyte colony-stimulating factors] G-CSFs for mobilisation of stem cells in healthy donors is NOT recommended by the [European Group for Bone Marrow Transplants] EBMT'. The Panel did not consider that the statement misleadingly implied a stipulation as alleged. No breach of the Code was ruled.

The Panel noted that the complainant was further concerned that the representative was said to have told a senior nurse that the commissioning of Granocyte now came direct from the new NHS commissioning board and not from the local clinical commissioning groups. It appeared that the complainant had not been party to the interaction between the nurse and the representative. The Panel noted that Chugai had provided a link to the NHS England website and a screen shot to show that Granocyte was a medicine which was not reimbursed through national prices set in the National Tariff and directly commissioned (and reimbursed) by NHS England.

The Panel did not consider that the complainant had established that, on the balance of probabilities, the representative had given the senior nurse inaccurate information as alleged. The Panel ruled no breach of the Code. The Panel further noted that there was no evidence that Chugai had incorrectly briefed its representatives about Granocyte reimbursement. The Panel ruled no breach of the Code. With regard to the alleged interaction with the senior nurse, the Panel did not consider that the complainant had established that the representative had failed to maintain a high standard of ethical conduct. The Panel ruled no breach of the Code.

The Panel noted its rulings above and considered that there had been no breach of Clause 2 of the Code.

An anonymous, non-contactable haematologist from a district general hospital complained in general that pharmaceutical company representatives encouraged the use of medicines by referencing inaccurate information, both in relation to available pharmaceuticals and the changes to commissioning within the new NHS. The complainant referred in particular to a recent meeting with a Chugai Pharma representative who promoted the company's granulocyte colony-stimulating factor (G-CSF) - Granocyte (lenograstim)

Granocyte was indicated in adults, adolescents and children older than 2 years for the reduction of the duration of neutropenia in patients (with non myeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation and considered to be at increased risk of prolonged severe neutropenia, the reduction of the duration of severe neutropenia and its associated complications in patients undergoing established cytotoxic therapy associated with a significant incidence of febrile neutropenia and the mobilisation of peripheral blood progenitor cells, for patients as well as healthy donors.

COMPLAINT

The complainant explained that as a consultant haematologist he/she worked in a typical district general hospital and saw a broad range of industry personnel, many from the same company which was frustrating.

The complainant stated that he/she had recently seen a Chugai representative; as the two had met before, the complainant hoped that the representative would know the complainant's workload very well. Yet despite previous conversations and knowing that the complainant's trust referred all patients who required stem cell transplants to the local teaching hospital, the representative insisted on showing the complainant an electronic slide show on his/her iPad to demonstrate the benefits of using G-CSF in healthy donors (relatives who gave their stem cells to assist a family member). When the complainant reminded the representative that the trust did not do any stem cell transplants, the representative replied 'If you see these types of results in healthy donors do you not agree that you would expect to see the same in your patients with neutropenia?'

The complainant was concerned that: the representative had not grasped the complainant's workload and the fact that transplant patients were referred to another centre; showing information at a non-transplant centre was of no benefit to the complainant and wasted both the representative's and complainant's time; the meeting was a tick box exercise to demonstrate to the representative's manager that he/she had seen the complainant; the Chugai data showed a recommendation from the European Group for Blood and Marrow Transplants (EBMT) which was a recommendation not a stipulation and as experts in their field, relevant clinicians should be given due respect to use whatever they deemed appropriate; the representative implied that extrapolation of data to fit another criteria was possible which was unethical, especially as patients with neutropenia were ill (normally with cancer) and had been treated with chemotherapy or radiation and healthy donors were fit and well; the representative could not show evidence that Granocyte was effective in patients with neutropenia when asked.

At the beginning of the conversation it was clear that the use of the electronic information was tracked and so the complainant queried whether this meant that representatives just had to see the complainant as a tick box exercise to keep his/her manager happy with no regard for what consultants really did or what was important. If there was new, factual and evidence based information then the complainant wanted to be informed otherwise he/she did not want his/her time wasted.

The complainant also alleged that other information which the representative had discussed with other members of the trust was incorrect. The complainant noted that a few weeks previously one of the senior nurses had asked him/her why the trust did not use Chugai's medicine as the representative had told her that the commissioning of Granocyte now came direct from the new NHS commissioning board and not from the local clinical commissioning groups (CCGs), this meant that whatever was prescribed within the trust would be reimbursed in full. Historically the local primary care trusts (PCTs) picked up the charge and asked the trust to switch to a generic product.

The complainant was concerned that the information was incorrect and gave a false impression of the reality. The complainant was informed by the finance director that 'we were urged by our local PCTs in 2012/2013 to switch away from branded prescribing where we were able to demonstrate a cost saving at every opportunity – today the new NHS commissioning board are asking us to only use branded products with exception as cost savings are essential to the new NHS'. The complainant was further concerned that the Chugai representative was not aware of the real facts and gave out incorrect information which came from head office as it was not aware of the real NHS and commissioning process.

The complainant appreciated that pharmaceutical companies were under pressure to maintain sales in what must be a very competitive market, but to do this by blatant extrapolation and twisting of the truth showed a new level within the UK which must be stopped immediately.

The complainant hoped that an investigation into this sort of practice would ensure that in future he/she and his/her colleagues were visited with only useful factual information and that they were not just a tick box exercise to satisfy a manager.

When writing to Chugai the Authority asked it to respond in relation to Clauses 2, 9.1, 7.2, 7.4, 15.2 and 15.9.

RESPONSE

Chugai noted that the complaint was anonymous, non-contactable and had not submitted any evidence or material to support his/her complaint.

Chugai took these allegations extremely seriously. All staff were aware of their need to maintain high standards between themselves and health professionals in line with the Code.

1 Interaction between the complainant and a Chugai representative

Chugai explained that Granocyte was indicated in adults, adolescents and children older than 2 years for:

- The reduction of the duration of neutropenia in patients (with non myeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation and considered to be at increased risk of prolonged severe neutropenia
- The reduction of the duration of severe neutropenia and its associated complications in patients undergoing established cytotoxic therapy associated with a significant incidence of febrile neutropenia
- The mobilisation of peripheral blood progenitor cells, for patients as well as healthy donors.

This complaint encompassed two alleged interactions that pertained to the indications for Granocyte:

- District general hospitals used Granocyte and other G-CSFs to treat patients with chemotherapy-induced neutropenia. The main treating physician was typically a consultant haematologist or oncologist
- In addition, tertiary care units used Granocyte and other G-CSFs to mobilise stem cells in patients and healthy donors. Subsequent follow-on care of these transplant patients was typically managed by a haematologist at a district general hospital.

Aligned to the above treatment pathways there were a number of reasons for a representative to see a haematologist in a district general hospital. Chugai representatives directly promoted the use of Granocyte to haematologists for use in neutropenic patients and to haematologists who might refer patients to specialist transplant units.

Chugai submitted that the anonymous nature of the complaint, the failure to identify a hospital or a geographical location, or to name the representative, placed Chugai in a difficult position. This complaint could emanate from any consultant haematologist working in the UK. In order to provide an appropriate response the company's compliance officer and its medical director conducted interviews with all of the representatives who promoted Granocyte; all of those interviewed denied any conversation with a consultant haematologist that could have led to this complaint. Furthermore the representatives refuted extrapolating clinical data in the donor population to data in the neutropenic patient setting. All of the representatives had passed the ABPI representative examination and certificates were provided.

In the context of this background information Chugai addressed the six specific items identified by the complainant. The comments were in relation to the alleged actions of the representative and Chugai had addressed the response in that context.

1 The representative had clearly not grasped the complainant's workload and the fact that transplant patients were referred to another centre. At a non-transplant centre, showing information that was of no benefit to the complainant wasted both the representative's and complainant's time.

As indicated earlier there were a number of reasons why Chugai representatives would visit haematologists in a district general hospital to promote Granocyte. There was nothing to suggest that any representative had acted inappropriately or visited an inappropriate customer. During the interviews with the representatives, each had been asked whether they were aware of a customer who had raised any concerns of this nature. No representative could identify any such concerns. Chugai submitted that in the absence of more specific detail it was unable to investigate further; there was no evidence that any representative had acted inappropriately or wasted a customer's time. The company refuted any breach of Clauses 9.1 and 15.2 in this regard.

2 The meeting was a tick box exercise to demonstrate to the representative's manager that he/she had seen the complainant.

Chugai submitted that it had no key performance indicator or required metric which compelled representatives to visit any health professional a specific number of times and it strongly adhered to the Code in that respect. Data collated from the e-sales aid recorded regional use only. Chugai stated that it collated this information so that it could see which pages of the e-sales aid the representatives used and in turn make it more appropriate and useful to its customers. Chugai denied that the use of the e-sales aid was a tick box exercise, and it refuted any breach of Clauses 9.1 and 15.2.

3 The Chugai data showed a recommendation from the EBMT; this was a recommendation not a stipulation so as experts in their field, relevant clinicians should be given due respect to use whatever they deemed appropriate.

Chugai stated that the e-sales aid contained the following quotation from EBMT: 'The use of biosimilar G-CSFs for mobilization of stem cells in healthy donors is not recommended by the EBMT'. This quotation clearly referred to healthy donors. Chugai recognised the expertise of health professionals to use whatever therapy they deemed appropriate, however the Code allowed industry to

use quotations from reputable bodies such as EBMT. There was no evidence that a representative had stipulated otherwise. Chugai refuted any breach of Clauses 9.1 and 15.2 in this regard.

4 Extrapolation of data to fit another criteria was unethical, especially as patients with neutropenia were ill (normally with cancer) and had been treated with chemotherapy or radiation. Healthy donors were fit and well. To suggest a similar outcome was unethical and unfounded.

Chugai categorically agreed that extrapolation of data from healthy donors to patients undergoing cancer treatment was neither ethical nor correct. Neither the e-sales aid nor the briefing document stated that efficacy results in one population were transferable to another. Chugai submitted that during the interview process all representatives denied any such conversation had taken place. In the absence of any evidence Chugai refuted any breach of Clauses 7.2, 7.4, 9.1 and 15.2 in this regard.

2 Granocyte Funding

Chugai submitted that the core concern was whether Granocyte reimbursement was provided by NHS England or the local CCG.

A link was provided to the NHS England website. This showed the latest version of its directly-purchased products list. Chugai provided a screen shot (using the spreadsheet filters) to show that Granocyte was on the list. This confirmed that Granocyte was reimbursed by NHS England.

In light of this Chugai refuted that any incorrect information was disseminated by its representatives.

Finally, Chugai noted its concern that the complainant was anonymous and non-contactable and had not supplied any evidence or material to support his/her serious allegations. Chugai was very concerned that this allegation could damage its good reputation.

PANEL RULING

The Panel noted the clauses cited by the case preparation manager, Clauses 2, 7.2, 7.4, 9.1, 15.2 and 15.9 of the Code. The 2014 Code came into operation on 1 January 2014 with a transition period for newly introduced requirements. The clauses cited in this case were the same in the 2014 and 2012 Second Edition (amended) Codes, thus the Panel used the 2014 Code.

The Panel noted that extreme dissatisfaction was usually required on the part of an individual before he/she was moved to complain. The Panel considered that Chugai was in a difficult position given that the complainant was anonymous and had not identified a hospital or a geographical location or named the representative. The complaint could have emanated from anywhere in the UK. The Panel noted that in order to provide an appropriate response Chugai's compliance officer and its medical director had interviewed all of the representatives who promoted Granocyte (ten) and provided copies of, *inter alia*, the Granocyte e-sales aid, and the relevant briefing document. Conversely, the complainant, who had the burden of proving his/her complaint on the balance of probabilities, had not provided any material to support his/her allegations. As the complainant was non-contactable, it was not possible to obtain more information from him/her. A judgement had to be made on the evidence provided by the parties.

The Panel noted the allegation that the representative had wrongly suggested that data from healthy donors could be extrapolated to the treatment of neutropenic patients. Chugai agreed that such extrapolation was neither ethical nor correct. The Panel noted that neither the e-sales aid nor the briefing document implied directly or indirectly that such extrapolation was possible. In that regard the Panel did not consider that the briefing material advocated a course of action which would be likely to lead to a breach of the Code and ruled no breach of Clause 15.9. Bearing in mind the materials used by the representatives, the Panel considered that, on the balance of probabilities, the complainant had not demonstrated that the unidentified representative had made a claim that data from healthy donors could be extrapolated to neutropenic patients. No breach of Clauses 7.2 and 7.4 were ruled.

The Panel noted Chugai's submission that, in district general hospitals, its representatives promoted Granocyte for use in patients with chemotherapy-induced neutropenia. Although the use of Granocyte to mobilise stem cells in patients and healthy donors was more likely in tertiary units, subsequent care of such patients was typically managed at the district general hospital. In the Panel's view it was thus not unreasonable that haematologists in secondary care might be informed about the use of Granocyte in tertiary units. In that regard, based on the material before it, the Panel did not consider that the representative in question had failed to maintain a high standard of ethical conduct by wasting the complainant's time as alleged. No breach of Clauses 9.1 and 15.2 was ruled.

The Panel noted that the e-sales aid contained the statement 'The use of biosimilar G-CSFs for mobilisation of stem cells in healthy donors is NOT recommended by the EBMT'. The Panel noted the complainant's concern that the statement from the EBMT was a recommendation and not a stipulation and that, as experts in their field, relevant clinicians should be given due respect to use whatever they deemed appropriate. The Panel considered that the statement in the e-sales aid clearly reported a recommendation and it noted the complainant's acknowledgement that the e-sales aid showed a recommendation from the EBMT. The Panel did not consider that the statement misleadingly implied a stipulation as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant was further concerned that the representative was said to have informed one of the senior nurses that the

commissioning of Granocyte now came direct from the new NHS commissioning board and not from the local CCGs. It appeared that the complainant had not been party to the interaction between the nurse and the representative. The Panel noted that Chugai had provided a link to the NHS England website and a screen shot to show that Granocyte was a medicine which was not reimbursed through national prices set in the National Tariff and directly commissioned (and reimbursed) by NHS England.

The Panel did not consider that the complainant had established that, on the balance of probabilities, the representative had provided a senior nurse with inaccurate information about the reimbursement of Granocyte as alleged. The Panel ruled no breach of Clauses 7.2 and 7.4. The Panel further noted that there was no evidence that Chugai had incorrectly briefed its representatives about Granocyte reimbursement. The Panel ruled no breach of Clause 15.9. With regard to the alleged interaction with the senior nurse, the Panel did not consider that the complainant had established that the representative had failed to maintain a high standard of ethical conduct. The Panel ruled no breach of Clauses 15.2 and 9.1.

The Panel noted its rulings above and considered that there had been no breach of Clause 2 of the Code.

Complaint received **6 March 2014**

Case completed **11 April 2014**

CASE AUTH/2704/3/14

MEDICINES MANAGEMENT PHARMACIST v FLYNN PHARMA

Circadin journal advertisement

A medicines management pharmacist referred to a claim in a Flynn Pharma Ltd advertisement in Prescriber for Circadin (melatonin) that 'Current guidance states that, when a hypnotic is indicated in patients aged 55 and over, prolonged-release melatonin should be tried first'. The claim was referenced to Wilson *et al* (2010) which the complainant stated was the 'British Association for Psychopharmacology [BAP] consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders'. The complainant alleged that this was hardly current guidance and was misleading as he/she was sure most others would take 'current guidance' to mean that recommended by the National Institute for Health and Care Excellence (NICE) or the All Wales Medicines Strategy Group (AWMSG) in Wales.

The detailed response from Flynn Pharma is given below.

The Panel noted that the complainant stated he/she interpreted the claim to mean guidance recommended by NICE or AWMSG in Wales. The Panel queried how many readers would similarly interpret the claim as such.

The Panel noted that Wilson *et al* was a consensus statement written by eighteen members of BAP. The Panel was unsure of the criteria used to select the authors and noted that guidance from a nationally recognised body was different from that issued by a small consensus group of eighteen members. However, the abstract referred to the document as the 'The British Association for Psychopharmacology guidelines'. The process for agreeing the final document was described in the abstract which stated 'All comments were incorporated as far as possible in the final document which represents the view of all participants although the authors take final responsibility for the document'. BAP published the Journal of Psychopharmacology in which the guidelines appeared. The advertisement at issue included a reference but this did not refer to BAP; only the publication details were cited.

The Panel noted Flynn Pharma's submission that it had played no part whatsoever in the process by which BAP selected the therapy area (insomnia), or formulated its consensus statement and guidelines. The Panel further noted that Flynn Pharma had taken over marketing responsibility for Circadin from Lundbeck in January 2012. The BAP guidelines were published in 2010 following a consensus meeting in May 2009. The Panel noted that although Flynn Pharma had no relationship with BAP, Lundbeck was one of two companies which provided unrestricted grants to partially offset the costs of the BAP consensus statement meeting. The 'method' section of the document explained that observers from the companies were invited to attend but did not participate in the summary proceedings or in drafting the guidelines. The funding arrangements were described on the final page which included 'The costs of the meeting were partly defrayed by unrestricted educational grants from two pharmaceutical companies (Lundbeck and …)'. The Panel further noted Flynn Pharma's submission that one of the authors was a lead investigator in the clinical development of Circadin.

The Panel considered that the claim at issue 'Current guidance states…' was not sufficiently clear that the recommendation came from the 'British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders' nor did it reflect the status of that document and the role of the marketing authorization holder at the time the document was produced. The use of the term 'current guidance' in this context gave insufficient information about the nature and status of the guidance such that the claim at issue was ambiguous and therefore misleading. The Panel considered that on the information provided in the advertisement it was likely that readers would assume that the guidance had been issued by a nationally recognized body such as NICE or AWMSG. That was not so. The Panel ruled a breach of the Code.

A medicines management pharmacist complained about an advertisement (ref Circ/ADV/13/0483) for Circadin (melatonin) placed in Prescriber, Vol 25 issue 1/2 January 2014, by Flynn Pharma Ltd.

Circadin was indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients aged 55 or over.

COMPLAINT

The complainant referred to a claim in the advertisement that 'Current guidance states that, when a hypnotic is indicated in patients aged 55 and over, prolonged-release melatonin should be tried first'. The claim was referenced to Wilson *et al* (2010).

The complainant alleged that this was misleading as he/she was sure most others would take 'current guidance' to mean that recommended by the National Institute for Health and Care Excellence (NICE) or the All Wales Medicines Strategy Group (AWMSG) in Wales. The complainant stated

that on further investigation, he/she found that the reference was to the 'British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders'. The complainant alleged that this was hardly current guidance.

Flynn Pharma was asked to respond in relation to Clause 7.2 of the Code.

RESPONSE

Flynn Pharma submitted that the British Association for Psychopharmacology (BAP) guidelines remained 'current' in so far as they had not been revised or superseded by any other authoritative guidance in the management of insomnia. Wilson *et al*, published the BAP consensus statement on evidence-based treatment for insomnia, parasomnias and circadian rhythm disorders in 2010 which provided comprehensive statements to guide clinicians managing patients in primary or secondary care. BAP was an authoritative and long-standing professional group in the UK with a track record of producing guidance in a number of areas of psychopharmacology. A transparent and robust process in developing guidelines, and in dealing with industry relationships, sponsorship and declarations of conflicts of interest was followed. Flynn Pharma submitted that the authors were convened to review the literature and identify the standards of evidence in their area, with an emphasis on meta-analyses, systematic reviews and randomised clinical trials, where available. The group developed consensus statements and guidance based on the evidence base available. The section 'Treatment of insomnia in the elderly' recommended 'when a hypnotic is indicated in patients over 55, prolonged-release melatonin should be tried first'. This was entirely consistent with the claim in question and the guidance remained current.

Flynn Pharma submitted that more recent published statements and advice reinforced the validity of the claim at issue. For example the British National Formulary (BNF) 66th Edition (September 2013), Section 4.1.1 Hypnotics, stated:

> 'Elderly. Benzodiazepines and the Z-drugs should be avoided in the elderly because the elderly are at greater risk of becoming ataxic and confused leading to falls and injury'.

Flynn Pharma submitted that this reinforced and strengthened prescriber advice in an important and more vulnerable patient population. Previous editions of the BNF included the following non-specific advice:

> 'Elderly. Hypnotics should be avoided in the elderly because the elderly are at a greater risk of becoming ataxic and confused leading to falls and injury'.

Importantly, in stipulating which hypnotics should be avoided in the elderly, the updated BNF, clarified to prescribers that this cautionary statement did not apply to prolonged-release melatonin (Circadin).

In October 2013, the Midlands Therapeutic Review and Advisory Committee (MTRAC) published commissioning support advice to primary care, on the use of Circadin, replacing a previous and negative recommendation from 2009. The new and current recommendation was positive ie melatonin was suitable for prescribing in primary care for the treatment of patients over the age of 55 with a diagnosis of primary insomnia, and for up to 13 weeks. The updated MTRAC advice was based on a comprehensive review which included BAP 2010 and a number of published papers not available to the BAP group at that time. This was a category A recommendation. This review supplanted the previous (January 2009), which was negative and based on a more limited evidence base. The remit of MTRAC was to review selected pharmaceutical products to assess their clinical value, safety and suitability for use in primary care, and to support appropriate prescribing and commissioning. Guidance issued by MTRAC reflected the appropriateness of prescribing these products in the primary care setting, based on the best evidence available.

The approval of prolonged-release melatonin tablets 2mg, in June 2007, post-dated the last NICE technology appraisal in this therapy area (TA77, April 2004, Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia). Whilst NICE often operated on a five year period before reviewing and updating its advice, Flynn Pharma understood that the NICE guidance was currently on a 'static' list.

More recently, NICE issued Good Practice Guidelines 2012 (Developing and updating local formularies), NICE recommended that for medicines that had not yet been considered, (or had not received a positive recommendation), for use in the NHS through a NICE technology appraisal, that NHS organisations should use other sources of high-quality information when appraising a medicine. MTRAC and BNF were specifically cited by NICE as relevant sources. Both were more recent sources and entirely consistent with, and in accordance with, the BAP 2010 guidelines.

Flynn Pharma submitted that it played no part whatsoever in the process by which BAP selected the therapy area (insomnia), or formulated its consensus statement and guidelines. BAP published its advice in 2010 following a consensus meeting in May 2009. Flynn Pharma only assumed marketing responsibility for Circadin in January 2012, taking over this responsibility from Lundbeck, which was one of two companies which provided unrestricted grants to partially offset the costs of the BAP consensus statement meeting. Clearly Lundbeck had an interest in the therapy area at the time but Flynn Pharma did not consider that the BAP guidelines were compromised in any way on that basis.

Flynn Pharma submitted that it did not have any relationship with any of the guideline authors. Since assuming responsibility for Circadin in 2012, Flynn Pharma had made declared payments to two of the authors who had delivered sponsored presentations

on Flynn Pharma's behalf. One was a lead investigator in the clinical development of Circadin and the other was a recognised international expert in the management of sleep disorders. Flynn Pharma had no and had never had any business relationship with Lundbeck.

In conclusion, Flynn Pharma stated that BAP 2010 guidance continued to be valid today and was further supported by more recent advice from BNF and MTRAC. There was not and nor was there anticipated to be any relevant guidance from NICE. In Wales, AWMSG had not, and would not consider Circadin since the resource impact of the product lay outside its role and remit (ie it was covered by AWMSG exclusion criteria). Flynn Pharma submitted that in its view the advertisement was fully compliant with the Code and specifically complied with Clause 7.2.

PANEL RULING

The Panel noted the clause cited by the case preparation manager, Clause 7.2. The 2014 Code came into operation on 1 January 2014 with a transition period for newly introduced requirements. Clause 7.2 was the same in the 2014 and 2012 Second Edition (amended) Codes, thus the Panel used the 2014 Code.

The Panel noted that the complainant stated he/she interpreted the claim 'Current guidance states that, when a hypnotic is indicated in patients aged 55 and over, prolonged-release melatonin should be tried first' to mean guidance recommended by NICE or AWMSG in Wales. The Panel queried how many readers would similarly interpret the claim as such.

The Panel noted that the claim was referenced to Wilson *et al* and it appeared that the claim was taken from the consensus statement written by eighteen members of the British Association for Psychopharmacology (BAP). The Panel was unsure of the criteria used to select the authors and noted that guidance from a nationally recognised body was different from that issued by a small consensus group of eighteen members. However, the abstract referred to the document as the 'The British Association for Psychopharmacology guidelines'. The process for agreeing the final document was described in the abstract which stated 'All comments were incorporated as far as possible in the final document which represents the view of all participants although the authors take final responsibility for the document'. BAP published the Journal of Psychopharmacology in which the guidelines appeared. The advertisement at issue included a reference but this did not refer to BAP; only the publication details were cited.

The Panel noted Flynn Pharma's submission that it had played no part whatsoever in the process by which BAP selected the therapy area (insomnia), or formulated its consensus statement and guidelines. The Panel further noted that Flynn Pharma had taken over marketing responsibility for Circadin from Lundbeck in January 2012. The BAP guidelines were published in 2010 following a consensus meeting in May 2009. The Panel noted that although Flynn Pharma had no relationship with BAP, Lundbeck was one of two companies which provided unrestricted grants to partially offset the costs of the BAP consensus statement meeting. The 'method' section of the document explained that observers from these companies were invited to attend but did not participate in the summary proceedings or in drafting the guidelines. The funding arrangements were described on the final page of the document which included 'The costs of the meeting were partly defrayed by unrestricted educational grants from two pharmaceutical companies (Lundbeck and ...)'. The Panel further noted Flynn Pharma's submission that one of the authors was a lead investigator in the clinical development of Circadin.

The Panel noted Flynn Pharma's submission regarding MTRAC guidance. This was used as reference to another claim in the advertisement at issue; 'Melatonin (Circadin) is suitable for prescribing in primary care'.

The Panel considered that the claim at issue in the advertisement 'Current guidance states...' was not sufficiently clear that the recommendation came from the 'British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders' nor did it reflect the status of that document and the role of the marketing authorization holder at the time the document was produced. The use of the term 'current guidance' in this context gave insufficient information about the nature and status of the guidance such that the claim at issue was ambiguous and therefore misleading. The Panel considered that on the information provided in the advertisement it was likely that readers would assume that the guidance had been issued by a nationally recognized body such as NICE or AWMSG. That was not so. The Panel ruled a breach of Clause 7.2.

Complaint received **14 March 2014**

Case completed **30 April 2014**

CODE OF PRACTICE REVIEW – May 2014

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

2614/7/13	**Health professional v Allergan**	**Market Research**	**Two breaches Clause 3.1** **Breaches Clauses 3.2, 4.1, 9.1, 12.2 and 18.1** **Report from Panel to Appeal Board**	**Appeal by respondent**	**Page 3**
2640/9/13	Anonymous v Nicoventures	Call rates pre-licence	No breach	No appeal	Page 20
2643/10/13	**Anonymous contactable v Pharmaxis**	**Approval of material and provision of training**	**Breach Clause 2** **Three breaches Clause 14.3** **Breaches Clauses 9.1 and 14.1**	**Appeal by complainant**	**Page 24**
2644/10/13	Norgine v Galen	Prescribing policy for Laxido Orange	No breach	Appeal by complainant	Page 34
2645/10/13 and 2647/10/13	Patient v Amgen and GlaxoSmithKline	Patient information on Prolia	No breach	Appeal by complainant in Case AUTH/2645/10/13	Page 40
2646/10/13	**Anonymous Health professional v Merck Sharp & Dohme**	**Sponsorship of health screening**	**Breaches Clauses 9.1 and 9.10**	**No appeal**	**Page 57**
2650/11/13	**Pfizer and Bristol-Myers Squibb v Bayer**	**Promotion of Xarelto**	**Two breaches Clause 7.2** **Three breaches Clause 7.4** **Two breaches Clauses 7.10 and 9.1**	**No appeal**	**Page 63**
2651/11/13	Health professional v Merck Sharp & Dohme	Alleged promotion of unlicensed medicines	No breach	No appeal	Page 75
2653/11/13	**Novo Nordisk v Sanofi**	**Provision of insufficient data from head-to-head study**	**Breach Clause 7.2**	**No appeal**	**Page 82**
2679/11/13	Advertising agency employee v Bayer	Advertisement on a public website	No breach	No appeal	Page 89
2680/11/13	Advertising agency employee v Lilly	Advertisement on a public website	No breach	No appeal	Page 92
2681/11/13	Hospital doctor v GlaxoSmithKline	Invitation to exhibition stand	No breach	Appeal by respondent	Page 95
2682/11/13	**Anonymous v Merck Serono**	**Provision of hospitality**	**Breach Clause 9.1** **Two breaches Clause 19.1**	**No appeal**	**Page 100**
2697/1/14	Ex-employee v Novo Nordisk	Conduct of company employees	No breach	No appeal	Page 107
2698/1/14	**Voluntary admission by Astellas**	**Declaration of sponsorship**	**Breaches Clauses 9.1, 9.10 and 12.1**	**No appeal**	**Page 110**
2701/2/14	Anonymous General Practitioner v GlaxoSmithKline	Relvar advertisements	No breach	No appeal	Page 115
2703/3/14	Anonymous consultant haematologist v Chugai	Conduct of a representative	No breach	No appeal	Page 122
2704/3/14	**Medicines Management Pharmacist v Flynn Pharma**	**Circadin journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 127**