NUMBER 90 November 2015

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.

NEWLY OPTIMISED PMCPA WEBSITE

The optimisation project to make it possible to use www.pmcpa.org.uk on the move is now complete. The team has worked hard to make it as easy as possible to view and interact with the website on mobiles and tablets. There has been considerable debate around the menu, not only whether it should be called a hamburger or a doughnut, but also how easy it is to use. Do please let us have your comments and suggestions, both on topics for future blogs and also on ease of use.

DISCLOSURE UPDATE

In 2016 pharmaceutical companies will disclose details of certain transfers of value to healthcare professionals (HCPS), other relevant decision makers (ORDMS) and healthcare organisations (HCOS) made during 2015 on a central platform. Further details can be found in the ABPI Code (see Clause 24 and others) and on the ABPI website. The Disclosure template can be found on the front page of the PMCPA website.

Recently further details about the arrangements were sent to pharmaceutical companies – including the data sharing agreement. Companies which have not done so already need to sign and return the data sharing agreement to the ABPI as soon as possible.

ADVISORY BOARDS

The President of the ABPI and the Director of the PMCPA have recently highlighted the need to ensure that advisory board meetings meet the requirements of the Code. These communications and advice on advisory boards are published on the PMCPA website.

THE 2016 CODE

Proposals for amendment of the ABPI Code and the PMCPA Constitution and Procedure were agreed at the Half Yearly Meeting of the ABPI on 11 November.

In October when reviewing the consultation responses the ABPI Board of Management decided that there should be a further consultation in relation to requirements to certify meetings involving travel outside the UK. In addition, further supplementary information should be added to the Code regarding disclosure of transfers of value. This consultation closed on 12 November. The final proposals were agreed at a special ABPI General Meeting on 1 December.

The changes to the Code come into operation on 1 January 2016 but, during the period 1 January to 30 April, no promotional material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of newly introduced requirements.

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

* FINAL REMINDER *

ABPI unaccredited examination ends

Clause 16.3 of the Code requires representatives to take an appropriate examination within their first year of employment and pass it within two years. The ABPI has been offering both the unaccredited examination and the more recently introduced accredited examination. The Code requires that representatives who commenced work on or after 1 October 2014 must take the accredited examination. It was also recommended that representatives commencing work on 1 January 2014 also take the accredited examination. The unaccredited ABPI examination finishes in December 2015. Staff currently studying for this examination need to be entered for the examination in December and pass it. From 1 January 2016 the ABPI will only offer the accredited examination.

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 dates on which places remain available are:

Monday 25 January
Thursday 3 March

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.

EXEMPTIONS TO CLAUSE 1.2 OF THE CODE

Clause 1.2 defines the terms 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'. These are a number of exemptions to this clause including that 'information supplied by pharmaceutical companies to national public organisations, such as the National Institute for Health and Care Excellence (NICE). The All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) is exempt from the Code provided the information is factual, accurate and not misleading'. There are thus two elements to this exemption, ie the body to which the information is directed has to be a national public organisation similar to NICE etc and the information has to be factual, accurate and not misleading. The Authority has recently considered two cases which touched upon the first element.

Although the list of organisations given in the exemption is not exhaustive and other closely similar bodies might be recognised as national public organisations, the exemption should be narrowly construed. From the cases considered so far, the Authority has taken the view that for an organisation to be sufficiently similar to NICE etc then any decision it makes should be publicly available and the organisation should have no commissioning powers or procurement/budgetary responsibilities. If these criteria are not satisfied (and there may be others to consider) then it is possible that the first element of the exemption will not have been met and any information given to such organisations by pharmaceutical companies will be subject to the Code.

Case AUTH/2754/5/15

ANONYMOUS, NON-CONTACTABLE NURSE v MERCK SERONO

Call frequency

An anonymous, non-contactable complainant who described themselves as a senior multiple sclerosis (MS) nurse specialist in an NHS trust, complained about the frequency with which Merck Serono sales representatives came to see him/her, often without an appointment. This was made more inconvenient by the various people they frequently brought with them. The complainant stated that although he/she had repeatedly objected to the additional visitors, the visits had not only continued but actually increased. The complainant noted that his/her colleagues had reported similar issues with the company.

The detailed response from Merck Serono is given below.

The Panel noted that market research commissioned by Merck Serono had shown that customers were being called on more frequently by competitors. In response the company created a sales team incentive as a 'short term fix' for the whole of March 2015 to help the team achieve a target of 6 contacts/day with all MS customers, including MS specialist nurses. Merck Serono submitted that this had a positive effect on the sales teams.

The Panel noted the contact and call rates with MS nurses and neurology customers submitted by the company. The percentage solicited calls with all neurology customers varied between 96% and 100% from November 2014 to March 2015. The Panel noted that the percentage of solicited calls during March was 98%, the second lowest percentage of solicited calls during the six-month period from November 2014 to April 2015. An increase was also seen in the market research findings of the frequency of visits to MS specialists from January to March 2015.

The Panel noted the complainant's concern about the frequency with which the representative came to see him/her, often without an appointment. In the Panel's view the data provided by the company was consistent with the complainant's comment that calls were of increasing frequency.

The Panel noted that a communication sent in December 2014 to the key account managers (KAMs) stated that a key performance indicator for 2015 was 3 contacts/day. The customer target spreadsheet created by the KAMs referred 'to no more than 3 unsolicited calls per customer in line with ABPI Code'.

The Panel noted that an incentive scheme was generally understood to, *inter alia, encourage* increased productivity; it was therefore not a mandatory requirement. Merck Serono provided several emails to the sales team sent on 30 April 2015. It was of concern that, contrary to Merck Serono's submission that the incentive scheme ran during March 2015, the emails showed that, at the very least, it had continued throughout April and KAMs were expected to continue to achieve 6 contacts/day thereafter. The emails linked the contact rate of 6 per day to the team's business objectives for 2015. In the Panel's view, the KAMs had been given the impression that the contact rate of 6 per day applied not only to March 2015 but to the rest of the year. Each KAM had 50-60 MS specialists in their territory which meant each specialist would need to be contacted, on average, 2-3 times/month. The Panel considered this appeared to be a high contact rate.

The Panel considered that the KAMs appeared to have been given little comprehensive and consistent guidance on how to achieve 6 contacts/day and comply with the Code. This was a significant omission. The Panel was concerned that the terminology used in the emails about contacts and calls which was sent to certain KAMs on 30 April was inconsistent; in response to a specific request Merck Serono had been unable to provide its definition of call and contact rates and associated representatives' briefing. Solicited calls were only described in the briefing to KAMs on how to enter their contact rate in the CRM system. The Panel noted the company's submission that it was able to distinguish between call and contact rates on its in-house data system but considered that this did not alter the fact that the KAMs had not been adequately advised in this regard.

The Panel noted its comments above. The Panel noted that the March incentive scheme was, in reality, a requirement. The Panel considered that achieving this would mean that, on the balance of probabilities, the representatives would breach the Code; in the absence of consistent terminology and briefing on how to achieve 6 contacts/day and remain compliant with the Code, the frequency of representatives' calls would cause inconvenience. On the balance of the evidence breaches of the Code were ruled.

The Panel noted Merck Serono's submission that the sales team also recorded accompanied visit data, to the best of its knowledge all such visits were infrequent and pre-arranged with the MS specialist involved. Merck Serono provided data on accompanied calls. Merck Serono further submitted it was unaware of any trusts/hospitals which did not allow visitors and was equally unaware of any breaches or potential breaches of trust policies in the period January 2014 to April 2015. The Panel noted any breach of trust policy was a serious matter. The complainant had not provided a copy of

the relevant trust policy. The Panel considered that there was no evidence to support the allegation that a trust policy had been breached; the complainant bore the burden of proof in this regard. The Panel therefore ruled no breach of the Code.

An anonymous, non-contactable complainant who described themselves as a senior multiple sclerosis (MS) nurse specialist in an NHS trust complained about the call frequency of Merck Serono Limited's sales representatives.

COMPLAINT

The complainant noted that in previous years he/she had enjoyed a very cordial relationship with Merck Serono; the company had been very supportive of both him/her and his/her unit, but increasingly over the last few months the complainant had found the activities of the company and its representatives overpowering.

The complainant stated that he/she was most concerned about the frequency with which the sales representative came to see him/her, often without an appointment. This was made more inconvenient by the various people they frequently brought with them, including managerial, medical, marketing and administrative staff. The complainant stated that he/she had repeatedly explained that he/she would rather not have these additional visitors as they added no value to clinical care, threatened patient confidentially and such visits were against trust policy; despite his/her requests the visits had not only continued, but actually increased.

The complainant noted that he/she had recently met with some fellow nurses at a UK nurse association who reported that they had experienced similar issues with Merck Serono and believed the problems to be part of a wider change in the company's sales and marketing policy.

The complainant noted that he/she had spoken with the hospital pharmacist about his/her concerns, and it was suggested that as he/she had already spoken to the Merck Serono representative and not seen any improvement, he/she should draw his/her concerns to the PMCPA's attention.

When writing to Merck Serono, the Authority asked it to respond in relation to Clauses 15.2 and 15.4 of the Code.

RESPONSE

Merck Serono stated that for many years it had benefitted from having an experienced, professional neurology sales team which currently consisted of eight key account managers (KAMs) and a manager. Their accounts covered approximately 385 MS specialist doctors and nurses throughout the UK and Ireland with approximately 33 MS specialist nurses in each territory. Merck Serono stated that it was unable to categorise the subgroup *senior* MS specialist nurse as it was unfamiliar with how this was defined in the NHS.

Merck Serono explained that for almost two decades there had been relative stability and minimal competition as limited therapeutic options for MS were available. In 2014 there was a significant change to the environment in a short space of time as several newly licensed MS medicines became available. This had negatively impacted the sales of Merck Serono's MS product, Rebif, (interferon beta-1a) which had previously led the market for many years. With the rise of competitor activity and an increasing pool of MS stakeholders, the sales force had been challenged to not only review its current activities with known MS customers (such as MS specialist nurses) but to contact a wider group which might be potential prescribers or influence the use of MS therapies.

According to internal market research performed in January 2015, customers were being called upon more frequently by competitors. Only 20% of the 30 MS specialists who took part in an online survey reported seeing a Merck Serono representative at least once a month. This appeared to signal an urgent need to increase the representatives' activities to remain competitive. Additionally, with regard to MS specialist nurses specifically, a significant downward trend was noticed in the performance of the team as measured by their average 'daily contact' rates, with 'contact' meaning solicited or unsolicited face-to-face, email and telephone contacts, as well as contacts at meetings. Between November 2014 and January 2015, the team's average daily 'contact' rate was as low as 0.82.

Merck Serono stated that to help address this concern, changes were made to the head office team including the recruitment of a new director from January 2015. A new sales campaign was launched and a time-limited incentive was offered to the sales team between 1 and 31 March 2015 inclusive, to help achieve a target of 6 contacts per day to all MS customers, including MS specialist doctors and nurses but also other MS stakeholders such as pharmacists and general neurologists.

The incentive was created as a 'short-term fix' to ensure Merck Serono remained competitive and to improve the team's average contact rate which was falling. It was clear that the 'contact' rates improved as a result. The average daily contact rates for the three months February to April 2015 increased to 1.29 from 0.82 in the preceding three months. Despite these changes, the percentage of solicited calls to MS nurses specifically remained consistently high between 97% and 99%. This suggested that conversely the number of unsolicited calls was low and in line with the requirements of the Code.

The team also recorded which Merck Serono personnel had accompanied them on customer visits. These might include head office staff such as managers, marketing and medical but never administrative staff. One of Merck Serono's strategic pillars that drove the competency model for all employees was to become more 'customer-focused'. As a result, the leadership team (ie managers, directors) were encouraged to occasionally accompany KAMs on visits to customers so that they had a better insight into the needs of health professionals and patients and understood how best Merck Serono could support their goals towards

improving patient care. Merck Serono provided details of the staff involved and the rationale for their respective visits. Merck Serono stated that, to the best of its knowledge, these visits were infrequent and always prearranged with the MS specialist involved.

Merck Serono stated that with regard to trusts/ hospitals which did not allow additional visitors, neither the head office team nor the sales force knew of any such rules being present. Between January 2014 and April 2015, Merck Serono had not been informed of any breaches or potential breaches to trust policies. On further questioning, none of Merck Serono's representatives recalled any conversations with their customers around problems with the increased frequency of contacts, or of potential breaches to trust policy as indicated by the complainant.

Based on the above, Merck Serono submitted that although recent initiatives had increased the number of customer contacts with representatives, the company had no reason to believe that such contacts had caused any inconvenience. The total recorded numbers of unsolicited calls by the representatives had remained compliant with the Code. Merck Serono submitted therefore that it had not acted in breach of Clause 15.4. Merck Serono had also no reason to believe that the representatives had not continued to demonstrate the high standard of ethical conduct required by the Code and Merck policies. Merck Serono thus denied a breach of Clause 15.2.

In response to a request for further information, Merck Serono submitted the following:

1 Briefings and communications regarding the incentive scheme:

Merck Serono submitted a copy of a letter which was sent to all the neurology KAMs which outlined the details and conditions of the bonus scheme.

2 Merck Serono's definition of call and contact rates, and solicited and unsolicited calls including associated communications and/or briefings. Also an explanation of how a solicited or unsolicited call was documented in Merck Serono's customer relationship management (CRM) system:

Merck Serono submitted an approved and certified copy of a briefing to the KAMs on how to enter their contact rate in the Merck Serono CRM system on which all KAMs were trained.

The briefing set out the mandatory information which was required to be completed by the KAMs for each of their contacts, including whether or not this was a 'solicited call'. The briefing included a clear definition of solicited calls (and by implication unsolicited calls). The briefing also reminded the KAMs that no more than three proactive, promotional calls per health professional could be made in a 12-month period.

The briefing did not set out a definition of call and contact rates. However, the system required the KAMs to record their contacts as either face-to-face meetings, meetings, telephone contact or email contacts. Using the type of interaction recorded on the CRM system, Merck Serono could distinguish between call and contact rates. Merck Serono stated that call rates included all KAMs' face-to-face meetings, and contact rates included all face-to-face meetings, contact at meetings, telephone and email contacts with customers.

3 Data on KAM contact and call rates on all neurology customers from November 2014 to March 2015:

Merck Serono submitted details of the KAMs' monthly average contact and call rates on all customers from November 2014 to March 2015. Merck Serono split the contacts according to those which related to purely to face-to-face meetings (call rate) and those related to all customer contacts, including face-to-face meetings, contacts at meetings, telephone or email contacts (contact rate).

The rates were marginally different to those supplied in Merck Serono's original response because the CRM system was a live system. Since Merck Serono last ran the analysis, a few more calls had been entered. The company believed that all relevant calls had now been fully entered onto the CRM system for the time period specified.

4 Data on KAM contact and call rates on MS nurses from November 2014 to March 2015:

Merck Serono submitted details of the KAMs' monthly average contact and call rates on MS nurses from November 2014 to March 2015 and the monthly number of contacts which were accompanied. The same distinction was made between call and contact rates as defined above.

When comparing the total contact and call rate on all neurology customers between November 2014 and March 2015, and the total contact and call rate on MS nurses only during the same period, the proportion of calls made to MS nurses represented 35% of the total number of calls made to all neurology customers. Also the proportion of all contacts made to MS nurses represented around 30% of the total number of contacts made to all neurology customers.

In response to a further request for information Merck Serono submitted that an email was sent to the KAMs which detailed the quarter 2 targets; these targets were based on new patient numbers achieved on a monthly basis as illustrated. The targets were set for each KAM and region as indicated by the initials for the 8 KAMs. The targets for quarter 2 were not based on health professional contact rates – these were used only during March, as previously indicated. This email was not certified as it related to an internal briefing on field force financial targets rather than a salesforce briefing *per se* on their promotional activities with customers. In addition, the letter detailing the KAM sales incentive scheme (dated 31st January) was not certified as it related to internal team financial targets and did not specifically detail field force activity with customers.

The letter outlined the financial aspects of the KAM bonus scheme and did not indicate activity and metrics on call or contact rates with health care providers.

The email dated 2nd May that was sent by a new senior director to the KAM team should have been reviewed and certified; the language and tone of the email would not have been approved by the company's signatories and would have been amended. Unfortunately, the briefing material had not been put through the approval process in this instance which was an oversight. Merck Serono stated that it had addressed this issue with a senior director (who was new in the post at the time) and had reminded the whole commercial team that all field force briefings, which detailed activity with customers, had to be reviewed and approved by its signatories for certification purposes before distribution to KAMs.

The impact that the incentive scheme and associated communication had had on the call/contact rates with health professionals (including MS nurses), as recorded in the CRM system were detailed in the resultant KAM call rates which were provided. The company had not collected any additional evidence that the email of 2 May had led to any KAM breaching the Code in relation to their activities with health professionals. In summary Merck Serono did not believe that this had led the KAM team to have breached Clauses 15.2, 15.4 and 15.9 of the Code.

PANEL RULING

The Panel noted the similarities between this case and Case AUTH/2756/5/15. The Panel, nonetheless, considered each case separately. The Panel noted that the complainant was anonymous and non-contactable. Like all complaints, anonymous complaints were judged on the evidence provided. The complainant bore the burden of proving his/her complaint on the balance of probabilities.

The Panel noted that Clause 15.4 required representatives to ensure that the frequency, timing and duration of calls on, *inter alia*, health professionals, together with the manner in which they were made, did not cause inconvenience. The supplementary information to that clause stated that companies should arrange that intervals between visits did not cause inconvenience. The number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. Thus although a representative might speculatively call upon or proactively make an appointment to see a doctor or other prescriber three times on average in a year, the annual number of contacts with that health professional might be more than that. The supplementary information to Clause 15.4 also advised that when briefing representatives companies should distinguish clearly between expected call rates and expected contact rates. Targets must be realistic and not such that representatives breached the Code in order to meet them.

The Panel noted that the complainant referred to the increasing frequency of representatives' visits over the last few months. The complaint was dated 30 April 2015. The Panel noted that Merck Serono had an incentive scheme for 2015 and had submitted that it had run a short-term incentive scheme in March 2015.

The Panel noted Merck Serono's submission that it had responded to recent changes in the MS therapy environment with various sales and marketing activities and changes to the head office team.

Merck Serono commissioned market research; an on line survey of 30 MS specialists, carried out in three monthly waves; January, February and March 2015. The data for January showed customers were being called on more frequently by competitors. To address this Merck Serono stated that it had created an incentive to the sales team as a 'short term fix' from 1 – 31 March 2015 inclusive to help the sales team achieve a target of 6 contacts per day with all MS customers, including MS specialist nurses. Merck Serono submitted that this had a positive effect on the sales teams.

The Panel noted that some of the contact/call rates provided in the company's responses to requests for further information differed from those provided in the company's initial response as the CRM system had been updated with further contacts. These differences did not, in the Panel's view, appear to be significant. Overall, the contact rate with MS nurses was 1.05 (May 2014), 1.0 (November 2014), 0.6 (December 2014), 0.8 (January 2015), 1.3 (February 2015) and 1.4 (March 2015). The corresponding call rates were 0.7, 0.6, 0.6, 0.9 and 1.2 from November 2014 through to March 2015. The percentage solicited calls with MS nurses according to the company's initial response dated 22 May 2015 was 98% (May 2014), 99% (November 2014) and 97% (February 2015). The monthly daily contact rate with all neurology customers was 2.9 (November 2014), 2.5 (December 2014), 2.4 (January 2015), 4.6 (February 2015), 5.2 (March 2015). The corresponding call rates were 1.8, 1.5, 1.5, 3.2 and 3.6 from November 2014 through to March 2015. The percentage solicited calls with such customers varied between 96% and 100% over the same period. The Panel noted that the percentage of solicited calls during March was 98%, the second lowest percentage of solicited calls during the six-month period from November 2014 to April 2015.

An increase was also seen in the market research findings with MS specialists which showed that the frequency of representatives' visits classified as 'often/once a month' was 50 in both March and February 2015 and 20 in January 2015. The frequency of representatives' visits classified as 'sometimes/every 3 months' was 30 in March 2015, 27 in February 2015 and 20 in January 2015.

The Panel noted the anonymous complainant's submission that the activities that he/she found most concerning were the frequency with which the sales representative came to see him/her, often without an appointment. In the Panel's view the data provided by the company was consistent with the complainant's comment that calls were of increasing frequency.

The Panel noted that a communication sent in December 2014 to the KAMs stated that a key performance indicator for 2015 was 3 contacts per day. The customer target spreadsheet created by the KAMs referred 'to no more than 3 unsolicited calls per customer in line with ABPI Code'.

The Panel noted that an incentive scheme was generally understood to be, amongst other things, a scheme which *encouraged* increased productivity; it was therefore not a mandatory requirement. Merck Serono provided several emails from a senior manager to the sales team sent on 30 April 2015, which included, *inter alia*,: 'Please can you let me know your plan to return activity to the required standard, I'd like to see improvements each week until 6 is achieved and please see that your activity levels are raised appropriately and urgently'. It was of concern that, contrary to Merck Serono's submission that the incentive scheme ran during March 2015, the aforementioned emails showed that, at the very least, it had continued throughout April and KAMs were expected to continue to achieve a contact rate of 6 per day thereafter. The emails linked the contact rate of 6 per day to the team's business objectives for 2015. In the Panel's view, the KAMs had been given the impression that the contact rate of 6 per day applied not only to March 2015 but for the remainder of 2015.

The Panel noted the neurology sales team currently consisted of 8 KAMs each of whom had approximately 385 MS specialist doctors and nurses in their territory, approximately 264 of whom were specialist nurses (33 per territory) with the remaining 121 being specialist doctors (15 per territory). This would mean each KAM would have approximately 48 specialists per territory. The Panel noted this was an approximation but was similar to the 50-60 MS specialists per territory submitted by Merck Serono in Case AUTH/2756/5/15. March 2015 had 22 working days, if a KAM was to achieve the 6 contacts a day this would give an overall contact volume of 132 contacts for that month. Each KAM had approximately 50-60 MS specialists in their territory which would mean each specialist would need to be contacted on average 2-3 times in the month. The Panel considered this appeared to be a high contact rate. The supplementary information to Clause 15.4 included that 'the number of calls made on a doctor or other prescriber and the intervals between successive visits are relevant to the determination of frequency. Companies should arrange that intervals between visits did not cause inconvenience'. The Panel further noted Merck Serono's MS medicine Rebif had been available for over ten years, and for the six months November 2014 to April 2015 the KAM team had an average of 98.5% of all contacts documented as solicited. It seemed odd that the percentage of solicited calls in March 2015 at 98% during the incentive scheme was the second lowest during the period November 2014 to April 2015. Merck Serono defined a solicited call within their CRM training document as a call where the health professional requested/solicited the visit.

The Panel considered that the KAMs appeared to have been given little comprehensive and consistent guidance on how to achieve 6 contacts/day and comply with the Code. This was a significant omission. The Panel was concerned that the terminology used in the emails about contacts and calls which was sent to certain KAMs on 30 April from a senior manager and a senior director was inconsistent. It was of concern that in response to a specific request the company had been unable to provide its definition of call and contact rates and associated representatives' briefing. The supplementary information to Clause 15.4 required companies when briefing representatives to clearly distinguish between expected call and contact rates. Solicited calls were only described in the briefing to KAMs on how to enter their contact rate in the CRM system. The Panel noted the company's submission that it was able to distinguish between call and contact rates on the CRM system but noted that such ability did not alter the fact that the KAMs had not been adequately advised in this regard.

The Panel noted its comments above. The Panel noted that the March incentive scheme was, in reality, a requirement. The Panel considered that achieving this would mean that, on the balance of probabilities, the sales representatives would breach the requirements of the Code; in the absence of consistent terminology and briefing on how to achieve the contact rate of 6 per day and remain compliant with the Code, the frequency of representatives' calls would cause inconvenience. On the balance of the evidence a breach of Clause 15.4 was ruled. The Panel noted the requirements of Clause 15.2 which stated, *inter alia*, that 'Representatives must at all times maintain a high standard of ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code'. The Panel noted the ruling above and on balance ruled a breach of Clause 15.2.

The Panel noted Merck Serono's submission that the sales team also recorded accompanied visit data, to the best of its knowledge all such visits were infrequent and pre-arranged with the MS specialist involved. Merck Serono provided data on accompanied calls: May 2014 -19 calls, November 2014 – 5 calls and February 2014 – 8 calls. Merck Serono further submitted it was unaware of any trusts/hospitals which did not allow visitors and was equally unaware of any breaches or potential breaches of trust policies between January 2014 and April 2015. The Panel noted any breach of trust policy was a serious matter. The complainant had not provided a copy of the relevant trust policy. The Panel considered that there was no evidence to support the allegation that a trust policy had been breached; the complainant bore the burden of proof in this regard. The Panel therefore ruled no breach of Clauses 15.2 and 15.4.

Complaint received **5 May 2015**

Case completed **24 July 2015**

CASE AUTH/2755/5/15

HEAD OF MEDICINES OPTIMISATION v A MENARINI

Promotion of Adenuric

A head of medicines optimisation complained about an email from A Menarini which was sent to payers, formulary committees, prescribing advisors and medicines management teams. It stated that the recent price increase [29%] for generic allopurinol might be important in relation to the potential increase in the long-term costs of treating hyperuricaemia associated with gout; an attached document which promoted Adenuric (febuxostat) (an alternative to allopurinol marketed by A Menarini) stated that if the current trend continued, the annual allopurinol expenditure would rise by approximately £2.6 million. A graph depicted the rise in allopurinol average unit cost.

The complainant alleged that the letter misrepresented the issues dramatically. To imply that long-term costs could be better planned or managed by using Adenuric (£24.36 for 28) vs allopurinol which had ranged from £1 to £1.40 over the last four years was irresponsible. From the start of the graph in 2011 at £1.20 an annual growth of around 4% meant the price would be, as currently, around £1.40. The complainant noted that the very large scale graph presented the minimal variation in allopurinol costs but not the cost of Adenuric. The complainant further noted that the price of Adenuric, in small type at the bottom of the prescribing information, was a long way from the larger type which highlighted the 29% increase in price for allopurinol.

The complainant provided a summary of prescribing data and costs (December 2014 – February 2015) which he stated showed balanced representation; the 61,242 allopurinol items dispensed, at a cost of £109,951 had increased recently, whereas the 1,320 Adenuric items, at a cost of £34,881 had remained fairly flat. The complainant stated that if A Menarini's advice was followed, and all patients on allopurinol were switched to Adenuric, net NHS expenditure would increase to £2,795,553 per quarter which would increase the category spend to £3million vs the current spend of £205,946. This was not a good use of NHS resources and might divert scarce resources from other conditions and treatments with more effective or efficient treatments.

The complainant also queried whether the email was a data breach to initially share the details with all the people copied in. There was a significant number of broken emails and legacy emails from organisations closed over two years ago.

The detailed response from A Menarini is given below.

The Panel noted the reference to the 29% increase in the average cost of allopurinol and that if the trend continued allopurinol expenditure would rise by approximately £2.6 million. Beneath the graphical representation of the price increase the text began 'Another ULT [urate lowering therapy] is Adenuric (febuxostat)'. The reader was told that further information about Adenuric could be viewed on the reverse of the item. The reverse featured the prescribing information. The Panel considered that given the emphasis on the financial impact of the recent price increase the material implied that Adenuric would be a suitable and a less expensive alternative. This was not so. The Panel noted that Adenuric (£24.36/28 tablets) was considerably more expensive than allopurinol (£1.43/28 tablets).

The Panel considered that the material was misleading about the relative costs of allopurinol and Adenuric, and the cost advantages that could be achieved by switching to Adenuric. The Panel was concerned that the material referred to a 29% increase in the unit cost of allopurinol without immediately quantifying the unit cost. The Panel was concerned that the reference to future allopurinol expenditure rising by £2.6 million was not robust and noted the complainant's comments in that regard. This misleading impression was compounded by references in the text to to planning for long-term expenditure. The Panel did not accept A Menarini's submission that the material provided bald information for the reader to make up their own mind. The cost information for Adenuric was not included other than in the prescribing information. The Panel considered the material including the graph was misleading and did not give a clear, balanced view of the position. Breaches of the Code were ruled as acknowledged by A Menarini.

The Panel noted the email was sent to the company's own mailing list. There was a difference of opinion between the parties as to the accuracy of the list. It was for the complainant to prove his case on the balance of probabilities. The Panel noted that the Code required companies to have prior permission from recipients when using email for promotional purposes. The Panel noted that A Menarini had had developed the email list from names suggested by its staff. The company had not shown it had prior permission to send promotional emails to those health professionals whose email addresses it had acquired. Such permission could not be implied either from possession of the email address or from a health professional not asking to be removed from the mailing list. The Panel did not consider that the requirements of the Code had been satisfied and a breach was ruled.

The email provided by the complainant had been sent to, what appeared to be, a primary care trust; these were replaced by clinical commissioning groups on 1 April 2013. On the material provided, the Panel did not consider that the complainant had demonstrated that the email had been circulated

to those who had no need for or interest in the content. No breach of the Code was ruled. However the Panel ruled a breach of the Code as it considered that the email list was not up-to-date.

The Panel did not consider the promotional nature of the email had been disguised; no breach of the Code was ruled. The Panel also ruled no breach of that part of the Code which referred to studies etc as it was not relevant to the mailing.

The Panel was concerned that the email addresses of all the recipients had been circulated to all on the list. The Panel queried whether permission had been given to pass on these details. The Panel was concerned about the nature of some of A Menarini's submissions including that the material contained bald information for the reader to make up their mind; its comments in relation to permission to receive promotional emails; and that there were no promotional claims or comparisons in the material. The Panel considered that such comments demonstrated a fundamental lack of understanding of the Code. The Panel noted the poor quality of the material and its rulings of breaches of the Code. The potential impact on NHS budgets if the changes were made was of serious concern. It considered that high standards had not been maintained and ruled a breach of the Code.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. On balance the Panel did not consider that the circumstances warranted such a ruling and thus it ruled no breach of Clause 2.

A head of medicines optimisation complained directly to A Menarini Farmaceutica Internazionale SRL about an email (6 May 2015) he had received from the company. The complaint was copied to the Authority.

The email in question was sent to payers, formulary committees, prescribing advisors and medicines management teams. The email consisted of a covering letter which stated that the attached information about the recent price increase for generic allopurinol might be important in relation to the potential increase in costs for the treatment of hyperuricaemia associated with gout. The attached promotional piece for Adenuric, (ref 5822/ADE/APR/2015/CRJ), headed 'Generic Bulletin – Urate Lowering Therapies [ULTs]', detailed a recent price increase for allopurinol and stated that the average unit cost had increased by 29% and that if the trend continued, the annual allopurinol expenditure would rise by approximately £2.6 million. The attachment stated that these developments had implications for those wishing to plan their long-term expenditure costs for ULTs and featured a graph showing the rise in allopurinol average unit cost. A Menarini marketed an alternative ULT, Adenuric (febuxostat) for the treatment of chronic hyperuricaemia. The attachment stated that Adenuric delivered a continuity of supply, price consistency and a clear level of clinical efficacy. Both allopurinol and Adenuric inhibited uric acid production.

The complaint was considered under the 2015 Code.

COMPLAINT

The complainant stated that he was pretty disgusted with the letter as it misrepresented the issues dramatically. To imply that Adenuric (£24.36 for 28) was a better way to manage or plan the long-term expenditure costs of urate lowering therapies, when allopurinol had ranged from £1 to £1.40 over the last four years was to completely miss the point. From the start of the graph in 2011 at £1.20 an annual growth of around 4% meant the price would be around the current £1.40 level. The complainant noted that the very large scale graph presented the minimal variation in allopurinol costs but not the cost of Adenuric; he assumed that this was because, while having a flat variation, it would be off the top of the page due to the scale used.

The complainant noted that the only reference to the price of Adenuric, in 8 point type at the bottom of the prescribing information, was a long way from the 11 point type which highlighted the 29% increase in price for allopurinol. The complainant stated that he supported the approval, in certain patients, of Adenuric by the National Institute for Health and Care Excellence (NICE), but he considered that to suggest that a product which was currently 1,740% higher than the newly higher price of allopurinol, should help manage 'long-term expenditure costs', was irresponsible.

The complainant provided a summary of the item, cost and cost per item to show a balanced representation. This showed that for December 2014 – February 2015 the 61,242 allopurinol items dispensed, at a cost of £109,951 had increased recently, whereas the 1,320 Adenuric items, at a cost of £34,881 had remained fairly flat. The complainant stated that if, in the unlikely and undesirable event that A Menarini's advice was blindly followed, and all patients on allopurinol were switched to Adenuric, the NHS would see a net increase in expenditure to £2,795,553 per quarter which would increase the category spend to £3million vs the current spend of £205,946. The £12million annual pressure would represent 2.4% of the primary care medicine budget in the complainant's geographical area – equivalent to the entire average uplift. This was not a good use of NHS resources and might divert scarce resources from other conditions and treatments with more effective or efficient treatments. The complainant cited Clauses 7.2, 7.8, 12.1 and 12.2 of the Code and stated that there might be others that applied.

The complainant also queried whether the email was a data breach to initially share the details with all the people copied in – many of whom he knew, others he did not. The complainant noted that there was a significant number of broken emails and legacy emails from organisations closed over two years ago. The complainant also alleged a beach of Clauses 11.1 and 11.3 of the Code.

When writing to A Menarini, the Authority asked it to respond in relation to Clauses 7.2, 7.8, 11.1, 11.3, 12.1 and 12.2 as cited by the complainant. The company was also asked to respond in relation to Clauses 2, 9.1 and 9.9.

RESPONSE

A Menarini noted the complainant's allegation that the email implied that Adenuric might be a better way of managing expenditure costs but submitted that this was, at best, debateable. The letter could as easily have been read as providing bald information for the reader to make up his/her own mind. It was probably a matter of personal interpretation.

A Menarini noted that the graph on page 1 showed that Adenuric was much more expensive than allopurinol. A Menarini acknowledged that it was misleading to show actual costs as there was a vast discrepancy between amounts of actual product sold. However, this was rectified by the cost per item, which redressed this. The graph of allopurinol on page 1 was in reality a flat graph simply showing the recent 29% increase. However, it was true that a 29% increase of not very much was still not very much. The graph itself was factual. The scale might be questionable. There was an implication that this might bring allopurinol closer to Adenuric but it seemed fairly clear that this was not so.

The price of Adenuric was illustrated only at the end of the prescribing information and this was an error and, although not technically misleading, could be interpreted as trying to hide information. A Menarini agreed that, to be fair, it should have been shown in direct comparison.

A Menarini submitted that although the information for the prescriber was there, it was not very clear and while it considered that it was unlikely that any recipient in the target audience would blindly take the action suggested by the complainant, it had to concede that the risk was there, albeit small.

A Menarini regrettably conceded that the email was not unambiguous and not correctly balanced; it was, however, accurate. The recipients could make their own decision, but not without some difficulty. A Menarini conceded breaches of Clauses 7.2 and 7.8.

A Menarini noted the complainant's suggestion that the recipients (which he knew about by open copy) might not have given permission for their names to be used and therefore be inappropriate. The list was taken from a short list held in-house by medical and held names suggested over time by senior field operatives. The names had been used on previous occasions and at every occasion, in upper case, the recipient was given the chance to be taken off the list. None of those circulated in this email had indicated this wish. Finally, it was believed that these recipients were all relevant to the message in the email. Whether the names should have been openly copied was debateable but A Menarini did not consider that to do so was damaging. The company denied a breach of Clause 11.

A Menarini did not agree that the material was disguised promotion. The promotional element seemed completely clear. The primary recipient, and all those by copy, was certainly within the category that was open to promotion (Clause 1.2), the piece was an email but did contain the necessary prescribing information. As an email it did not have an envelope as with older promotional activities but the header seemed entirely clear. The company denied a breach of Clause 12.

A Menarini noted that Clause 9 referred to taste and suitability. The company did not find anything in the email or its attachment that was distasteful. Furthermore the information contained (even accepting the opening response regarding Clause 7) was suitable for the recipients. A Menarini considered that the use of 'disgusted' was a loose one and depicted the complainant's strong disapproval rather than true 'disgust'.

A Menarini stated that whilst it agreed that it might have breached Clause 7, it did not consider that this had damaged the reputation of the industry as a whole. The email had its failings but was a 'one off' and it was not intended to repeat the exercise.

A Menarini denied a breach of Clauses 9 and 2 and stated that action had been taken to try to prevent a repetition of the accepted breach.

In response to a request for further information, and with regard to Clause 9.9, A Menarini stated that the email list was created by information received from its NHS relationships team using local knowledge and professional contact details. By virtue of having the email address of the recipient NHS customer the company understood that permission to communicate was implied and therefore this was in line with the Code. To support this understanding, this group of NHS customers had been corresponded with on two prior occasions and, as such, had been given the chance to withdraw from receiving such communications from A Menarini. To date, no requests to be removed from this form of communication by any of the customers had been received. A Menarini submitted that information like that in question was valuable for appropriate decision makers and noted that it made no promotional claims or comparisons in the material that was sent.

With regard to Clause 11.1, A Menarini stated that from its response in relation to Clause 9.9 above and in line with its understanding of the Code, the material was only sent to those persons reasonably assumed to be in need of, or interested in, receiving such correspondence. The profile of the recipients were all senior pharmacists or other relevant senior NHS decision makers. As such, the distribution list was appropriate.

With regard to Clause 11.3, A Menarini stated that the mailing list was compiled in June 2014 and as outlined above, this customer group had received two previous emails and had had at least two opportunities to withdraw from receiving such information. For the avoidance of doubt the wording to allow opt-out was:

> 'Please note, if you do not wish to receive such announcements in the future, please email me and you will be removed from our mailing list.'

To date, A Menarini had received no requests to be removed from this form of communication. The information was sent to 170 individuals with a total of 31 emails that were returned as undelivered. This was not an unexpected percentage.

A Menarini stated that as a result of this case, it had internally investigated its process with a view to refine and adjust as needed.

PANEL RULING

The Panel noted that the email provided by the complainant (dated 6 May 2015 at 10.05) was different to that provided by A Menarini (6 May 10.19) in that they had different circulation lists. The content was otherwise identical. The Panel noted the reference to the 29% increase in the average cost of allopurinol and that if the trend continued allopurinol expenditure would rise by approximately £2.6 million. Beneath the graphical representation of the price increase the text began 'Another ULT is Adenuric (febuxostat)'. The reader was told that further information about Adenuric could be viewed on the reverse of the item. The reverse featured the prescribing information. The Panel noted that the material had to be capable of standing alone in relation to compliance with the Code without reference to or qualification by the prescribing information. The Panel considered that given the emphasis on the financial impact of the recent price increase the material implied that Adenuric would be a suitable and a less expensive alternative. This was not so. The Panel noted that Adenuric at £24.36 for 28 tablets was considerably more expensive than the £1.43 for 28 allopurinol tablets (February 2015, figures provided by A Menarini).

The Panel considered that the material was misleading about the relative costs of allopurinol and Adenuric, and the cost advantages that could be achieved by switching to Adenuric. The Panel was concerned that the material referred to a 29% increase in the unit cost of allopurinol without immediately quantifying the unit cost. The unit cost figures in the graph did not assist as they were not in the same immediate visual field as the increased unit cost claim. The Panel was concerned that the reference to future allopurinol expenditure rising by £2.6 million was not robust and noted the complainant's comments in this regard. This misleading impression was compounded by referring to planning for long-term expenditure in the text. The Panel did not accept A Menarini's submission that the material provided bald information for the reader to make up their own mind. The cost information for Adenuric was not included other than in the prescribing information. The Panel considered the material including the graph was misleading and did not give a clear, balanced view of the position. Breaches of Clauses 7.2 and 7.8 were ruled as acknowledged by A Menarini.

The Panel noted the email was sent to the company's own mailing list. There was a difference of opinion between the complainant and A Menarini in relation to the accuracy of the list. The Panel noted that it was for the complainant to prove their case on the balance of probabilities. The Panel noted that Clause 9.9 required companies to have prior permission from recipients when using email for promotional purposes. A Menarini had not provided details of such prior permission despite being asked to do so. The Panel did not accept A Menarini's submission that by virtue of having the email address of the recipient NHS customer, permission to communicate was implied and therefore in accordance with the Code. The company had developed the list from names suggested by staff in the field. The company had not shown it had prior permission to send promotional emails to those health professionals whose email addresses it had acquired. Such permission could not be implied either by the fact that the company possessed the email address or that a health professional had not asked to be removed from the mailing list. The Panel did not consider that the requirements of Clause 9.9 had been satisfied and a breach was ruled.

The email provided by the complainant had been sent to, what appeared to be, a primary care trust; these were replaced by clinical commissioning groups on 1 April 2013. On the material provided, the Panel did not consider that the complainant had demonstrated that the email had been circulated to those who had no need for or interest in the content. No breach of Clause 11.1 was ruled. The Panel considered that the email list was not up-to-date and thus a breach of Clause 11.3 was ruled.

The Panel did not consider the email would be seen as anything other than promotional and was not disguised; no breach of Clause 12.1 was ruled. The Panel also ruled no breach of Clause 12.2 as this clause referred to studies etc and was not relevant to the mailing.

The Panel was concerned that the email addresses of all the recipients had been circulated to all on the list. The Panel queried whether permission had been given to pass on these details. The Panel was concerned about the nature of some of A Menarini's submissions including that the material contained bald information for the reader to make up their mind; its comments in relation to permission to receive promotional emails; and that there were no promotional claims or comparisons in the material. The Panel considered that these demonstrated a fundamental lack of understanding of the Code. The Panel noted the poor quality of the material and its rulings of breaches of the Code. The potential impact on NHS budgets if the changes were made was of serious concern. It considered that high standards had not been maintained and ruled a breach of Clause 9.1.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. On balance the Panel did not consider that the circumstances warranted such a ruling and thus ruled no breach of Clause 2.

Complaint received **6 May 2015**

Case completed **15 July 2015**

CASE AUTH/2756/5/15

ANONYMOUS EMPLOYEE v MERCK SERONO

Call rates

An anonymous employee complained about the call rates set by Merck Serono. The complainant noted that since a change of leadership in neurology in January 2015, the neurology sales team had been targeted to see six prescribing customers daily. Although this started off as an initial extra incentive in March 2015, it was now the required activity standard for the team. Each of the eight [sales] areas averaged 50-60 consultants and nurse specialists in multiple sclerosis (MS). The team was under pressure to achieve this with weekly reporting of activity; failure to achieve six calls/day resulted in the director emailing the individuals in question to ask for their plans to hit the required standard. Now the company response was 'there are other customers such as general neurologists, pharmacists, business unit managers', but previous experience calling on these customers had resulted in their referral back to the MS specialists. They did not want to see them often as they did not prescribe. The complainant noted that he/she respected his/her customers' time constraints and workload and so would not make unnecessary calls if it was of no benefit to the service they provided to their patients. The team was now under pressure to hit this target, a situation which had not arisen before. In the complainant's view this would lead to customers refusing to see representatives and perhaps disciplinary action being taken against individuals who refused to do what was required to achieve the new activity targets.

The detailed response from Merck Serono is given below.

The Panel noted that the complainant referred to an initial extra incentive in March 2015 which had now become the required activity standard. The Panel noted that Merck Serono had an incentive scheme for 2015 and had run an additional incentive for March.

The Panel noted Merck Serono's submission that over a short period of time there had been a significant change to the UK MS therapy environment as several newly licensed MS medicines had become available. This had negatively impacted the sales of Rebif (interferon beta 1a), which had been a leading product for over a decade. Merck Serono commissioned an online market research survey of 30 MS specialists, carried out in January, February and March 2015. The data for January showed customers were being called on more frequently by competitors. Merck Serono further submitted there had been a significant downward trend in the average 'contact' rates of the sales team; it responded to this with various sales and marketing activities and changes to the neurology head office team. To help deliver a new sales campaign the sales team were offered a time-limited incentive from 1 – 31 March 2015 inclusive of 30% of key performance indicators which would be paid on achieving a contact rate of 6 per day. Merck Serono submitted that this had a positive effect on the sales team's (key account managers (KAMs)) average daily contact rate.

The Panel noted that an incentive scheme was generally understood to, *inter alia, encourage* increased productivity; it was therefore not a mandatory requirement. Merck Serono had submitted several emails from a senior manager to certain members of the sales team sent on 30 April 2015. It was of concern that contrary to Merck Serono's submission that the incentive scheme ran during March 2015, the emails showed that, at the very least, it had continued throughout April and KAMs were expected to continue to achieve 6 contacts/day thereafter. The emails linked the contact rate of 6 per day to the team's business objectives for 2015. In the Panel's view, the KAMs had been given the impression that the contact rate of 6 per day applied not only to March 2015 but to the rest of the year.

An email from a senior director dated 2 May had not been certified and stated, *inter alia*, 'We really need achieve [sic.] 6 calls per day on prescribing customers' and referred to driving call volume and contact volume. There was no reference to the relevant requirements of the Code. The Panel noted Merck Serono's submission that the language and tone of the email would not have been approved by its signatories and would have been amended. No information was provided as to what would have been amended. Merck Serono further submitted that it had no evidence to show that the email of 2 May had led to any KAM breaching the Code in relation to their activities with health professionals. The Panel noted Merck Serono did not appear to have retracted or amended this email to the KAM team even though it had submitted that it would have been amended. The Panel was concerned that an email from the compliance department dated 11 May 2015 reminding staff that all representatives' briefings must be certified was sent after Merck Serono had been notified of this complaint on 7 May.

The Panel noted Merck Serono's submission that it was for each representative, as an experienced KAM to ensure that their chosen activities complied with the Code and were generally in line with the training they received. The Panel noted the email submitted by the complainant dated 20 March included the statement 'Please note all contacts must be made within the ABPI guidelines', a customer target spreadsheet reminded the representatives that 'Frequency of contacts to be decided by the activities on the target segment and must be reasonable, however no more than 3 unsolicited calls per customer in line with ABPI code. For the avoidance of doubt, please see Clause 15.4 of the code'. No such reminder was included in any of the

emails from the senior manager on 30 April or the email from the director dated 2 May.

The Panel considered that while Merck Serono had reminded its representatives that their activity should comply with the Code, it considered that the KAMs appeared to have been given little comprehensive and consistent guidance on how to achieve 6 contacts/day and comply with the Code. This was a significant omission. The Panel was concerned that the terminology used in emails about contacts and calls which was sent to certain KAMs on 30 April was inconsistent; in response to a specific request the company had been unable to provide its definition of call and contact rates and associated representatives' briefing. The Panel noted the company's submission that it was able to distinguish between call and contact rates on its in-house data system but considered that this did not alter the fact that the KAMs had not been adequately advised in this regard.

The Panel noted the neurology sales team currently consisted of 8 KAMs each of which had 50-60 MS specialists in their territory. March 2015 had 22 working days, if a KAM were to achieve the 6 contacts/day this would give an overall contact volume of 132 contacts for that month, which would mean each specialist in each territory would need to be seen on average 2–3 times in the month.

The Panel noted its comments above. The Panel noted that the March incentive scheme was, in reality, a requirement. The Panel considered that achieving this would mean that on the balance of probabilities the representatives would breach the Code; in the absence of consistent terminology and briefing on how to achieve 6 contacts/day and remain compliant with the Code, the frequency of representatives' calls would cause inconvenience. On the balance of the evidence breaches of the Code were ruled.

The Panel noted Merck Serono's submission that all representative briefing material was reviewed and certified. However the briefing material sent by the senior director, in March 2015 and submitted by the complainant had been sent to the representatives prior to certification. The Panel noted the email from the compliance department had been sent on 11 May. The Panel further noted in a subsequent submission by Merck Serono that the email dated 2 May 2015 headed 'Rebif Global Winning Team!' and provided by the complainant had not been certified. This was disappointing. The Panel noted its comments above regarding the date of the email from the compliance department about the need to certify all representatives' briefing material. A breach of the Code was ruled.

An anonymous, contactable employee complained about the call rates set by Merck Serono.

COMPLAINT

The complainant noted that since a change of leadership in neurology in January 2015, there had been a big push on activity where the neurology sales team had been targeted to see six prescribing customers daily. Although this started off as an initial extra incentive in March 2015, it was now the required activity standard for the team. Each of the eight [sales] areas averaged 50-60, at most, specialists in multiple sclerosis (MS) comprising MS consultants and MS nurse specialists. The team was under pressure to achieve this with weekly reporting of activity; failure to achieve six calls/day resulted in the director emailing the individuals in question to ask for their plans to hit the required standard. Now the company response was 'there are other customers such as general neurologists, pharmacists, business unit managers', but previous experience calling on these customers had resulted in their referral back to the MS specialists. They did not want to see them often as they did not prescribe. The complainant noted that he/she had provided a valuable service to his/her customers for many years, and he/she respected their time constraints and workload and so would not make unnecessary calls if it was of no benefit to the service they provided to their patients. The team was now under pressure to hit this target, a situation which had not arisen before in his/her many years with the company. In the complainant's view this would lead to customers refusing to see representatives and perhaps disciplinary action being taken against individuals who refused to do what was required to achieve the new activity targets. Before January 2015, activity was not a key focus, and never had been in the complainant's time with the company. The complainant provided documents which he/she considered clearly illustrated this drive on activity.

When writing to Merck Serono, the Authority asked it to respond in relation to Clauses 15.2, 15.4 and 15.9 of the Code.

RESPONSE

By way of background Merck Serono explained that all new and existing representatives underwent training to enable them to carry out their activities in the field in compliance with the Code and Merck Serono's policies. Training included face-to-face, web-based or 'read and understood' formats which were rolled out at induction with specific mandatory training as determined by internal policies. Merck Serono had for many years benefitted from having an experienced, professional neurology sales team which currently consisted of eight key account managers (KAMs) and a manager. Their accounts covered approximately 385 MS specialist doctors and nurses throughout the UK and Ireland with approximately 50-60 MS specialists in each territory.

Over the past year, and in a short space of time, there had been a significant change to the MS therapy environment due to several newly licensed MS medicines becoming available in the UK. This had negatively impacted the sales of Merck Serono's MS product Rebif (interferon beta-1a) which, until now, had been a leading product for over a decade. With the rise of competitor activity and an increasing pool of MS stakeholders that included MS nurses, general neurologists and specialist pharmacists, the representatives had been challenged to not only review their current activities with known MS customers but to contact a wider group who might

be potential prescribers or influence the use of MS therapies.

According to internal market research performed in January 2015, customers were being called upon more frequently by competitor companies. Only 20% of the 30 MS specialists who took part in the online survey reported seeing a Merck Serono representative at least once a month. This appeared to signal an urgent need to increase the representatives' activities to remain competitive. Additionally, a significant downward trend was noticed in the performance of the team as measured by its average 'contact' rates, with 'contact' meaning solicited or unsolicited face-to-face, emails and telephone contacts, as well as contacts at meetings. In quarter 3 2014 the team's average quarterly daily rate of 'contact' was 2.4/day. This contact rate was significantly lower than that achieved in quarters 1 and 2 of 2014.

To help address this concern, changes were made to the head office team which included the recruitment of a new director from January 2015 who initiated a new sales campaign. To help deliver this plan, a time-limited incentive was offered to the sales team to achieve a target of 6 contacts/day (within the above definition of 'contacts') between 1 and 31 March 2015 inclusive. This was highlighted in the email dated 20 March sent to the Authority by the complainant.

For the purpose of the target incentive scheme, a 'contact' was defined as a 'face-to-face' activity recorded within the customer relationship management (CRM) system or a 'meeting' activity where the customer was listed as 'attended' in the 'profiled attendees' part of the meeting module within the CRM. The incentive was created as a 'short-term fix' to ensure Merck Serono remained competitive and to improve the team's average contact rate which was falling. It was clear from the figures provided that the 'contact' rates improved as a result. The average daily contact rate was recorded at 2.2 in January 2015, 4.5 in February 2015 and 5 in March 2015. The daily contact rate for April 2015 was 3.5 illustrating that the incentive scheme was a short-term measure and achieved its objective.

The recorded numbers of unsolicited calls by representatives did not indicate a breach of Clause 15.4 as the average percentage of solicited contacts was between 96% to 99% over the period from quarter 1 2014 to quarter 2 2015. The majority of contacts involved pre-arranged or customer-requested presentations and follow-up meetings. It was never suggested in communications sent to the representatives that their activities should go beyond what was permissible under the Code. On the contrary, they were always reminded that such activity should be in line with the Code. It was therefore up to each representative, as an experienced KAM, to ensure that their chosen activities complied with the Code and were generally in line with the training they received. Merck Serono believed that it was possible to achieve the required target whilst remaining compliant with the Code, and no concerns were formally raised by any of the representative to a senior director. Therefore, Merck Serono had no reason to believe that its representatives had not continued to demonstrate the high standard of ethical conduct required by the Code and Merck Serono policies. Merck Serono denied a breach of Clause 15.2.

With regard to the requirements of Clause 15.9, it had always been Merck Serono's policy and practice to review and certify all representatives' briefing material according to the requirements of the Code. Recent examples of certified briefing materials to the salesforce were included for reference. All materials related to its new sales campaign were certified in accordance with such requirements. However, unfortunately, the briefing email sent on 20 March by the senior director and sent to the Authority by the complainant was sent to the team before certification.

Merck Serono submitted that it was clearly stated in its policies that materials were certified before distribution to the representatives and it regretted that this was not adhered to on this one occasion. This had been acknowledged and fully investigated by Merck Serono's compliance department which had consequently addressed the issue with the individuals involved. The compliance department had also reminded all head office staff of their obligation to ensure that all briefing material was approved and certified.

Merck Serono stated that it remained committed to ensuring all its activities were compliant within its policies and the Code.

In response to a request for further information Merck Serono submitted the following:

1 Briefings and communications regarding the incentive scheme:

Merck Serono submitted a copy of a letter which was sent to all the neurology KAMs in January 2015 which outlined the details of the bonus scheme.

2 Merck Serono's definition of all and contact rates, and solicited and unsolicited calls including associated communications and/or briefings. Also an explanation of how a solicited or unsolicited call is documented in Merck Serono's CRM system:

Merck Serono submitted an approved and certified copy of a briefing to the KAMs on how to enter their contact rate in the CRM system on which all KAMs were trained.

The briefing set out the mandatory information which was required to be completed by the KAMs for each of their contacts, including whether or not this was a 'solicited call'. The briefing included a clear definition of solicited calls (and by implication unsolicited calls) and also reminded the KAMs that no more than three proactive, promotional calls per health professional could be made in a 12 month period.

The briefing did not define call and contact rates. However, it required the KAMs to record their contacts as either face-to-face meetings, meetings, telephone contact or email contacts. Using the type of interaction recorded on the CRM system, Merck

Serono could distinguish between call and contact rates. Merck Serono stated that call rates included all KAMs' face-to-face meetings, and contact rates included all face-to-face meetings, contact at meetings, telephone and email contacts with customers.

3 Data on KAM contact and call rates on all neurology customers from November 2014 to March 2015:

Merck Serono submitted a chart that indicated the KAMs' monthly average contact and call rates on all customers from November 2014 to March 2015. Merck Serono split the contacts according to those which related to purely to face-to-face meetings (call rate) and those related to all customer contacts, including face-to-face meetings, contacts at meetings, telephone or email contacts (contact rate).

The rates were marginally different to those supplied in Merck Serono's original response. This was because the CRM system was a live system. Since Merck Serono last ran the analysis, a few more calls had been entered. Merck Serono believed that all relevant calls had now been entered onto the CRM system for the time period specified.

4 Data on KAM contact and call rates on MS nurses from November 2014 to March 2015:

Merck Serono submitted a chart that indicated the KAMs' monthly average contact and call rates on MS nurses from November 2014 to March 2015, as well as for each month the number of contacts which were accompanied. The same distinction was made between call and contact rates as defined above.

When comparing the total contact and call rate on all neurology customers between November 2014 and March 2015, and the total contact and call rate on MS Nurses only during the same period, the proportion of calls made to MS Nurses represented 35% of the total number of calls made to all neurology customers. Also the proportion of all contacts made to MS Nurses represented around 30% of the total number of contacts made to all neurology customers.

In response to a further request for information Merck Serono submitted that an email was sent by a senior manager to the KAMs which detailed the quarter 2 targets (copy provided); these were based on new patient numbers achieved on a monthly basis as illustrated. The targets were set for each KAM and region as indicated by the initials for the 8 KAMs. The targets for quarter 2 were not based on health professional contact rates – these were used only during the month of March, as previously indicated. This email was not certified as it related to an internal briefing on field force financial targets rather than a salesforce briefing *per se* on their promotional activities with customers. In addition, the letter detailing the KAM sales incentive scheme (dated 31st January) was not certified as it related to internal team financial targets and did not specifically detail field force activity with customers. The letter purely outlined the financial aspects of the KAM bonus scheme and did not indicate activity and metrics on call or contact rates with health care providers.

The email dated 2nd May that was sent by a new senior director to the KAM team should have been reviewed and certified. The language and tone of the email would not have been approved by the company's signatories and would have been amended. Unfortunately, this briefing material had not been put through the company's approval process in this instance which was an oversight. Merck Serono offered its assurance that it had addressed this issue with the senior director (who was new in the post at the time) and had reminded the whole commercial team that all field force briefings, which detailed activity with customers, had to be reviewed and approved by the signatories for certification purposes before distribution to KAMs.

The impact that the incentive scheme and associated communication had on the call/contact rates with health professionals (including MS nurses), as recorded in the CRM system, were detailed in the resultant KAM call rates which were provided. Merck Serono had not collected any additional evidence that the email of 2 May had led to any KAM breaching the Code. In summary, the company denied breaches of Clauses 15.2, 15.4 and 15.9 of the Code.

PANEL RULING

The Panel noted the similarities between this case and Case AUTH/2754/5/15. The Panel nonetheless considered each case separately. The Panel noted that the complainant was anonymous. Like all complaints, anonymous complaints were judged on the evidence provided. The complainant bore the burden of proving his/her complaint on the balance of probabilities.

The Panel noted that Clause 15.2 required that representative must at all times maintain a high standard of ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code, Clause 15.4 required representatives to ensure that the frequency, timing and duration of calls on, *inter alia*, health professionals, together with the manner in which they were made, did not cause inconvenience. The supplementary information to that clause stated that companies should arrange that intervals between visits did not cause inconvenience. The number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. Thus although a representative might speculatively call upon or proactively make an appointment to see a doctor or other prescriber three times on average in a year, the annual number of contacts with that health professional might be more than that. The supplementary information to Clause 15.4 also advised that when briefing representatives companies should distinguish clearly between expected call rates and expected contact rates. Targets must be realistic and not such that representatives breached the Code in order to meet them.

The Panel noted that the complainant referred to an initial extra incentive in March 2015 which had now become the required activity standard. The Panel

noted that Merck Serono had an incentive scheme for 2015 and had run an additional incentive for March 2015.

The Panel noted the complainant had submitted two emails in support of the allegations. The first dated 20 March 2015, subject: 'Additional Incentive!' was from a senior director and reminded the neurology sales team that 'for March 30% of KPI [key performance indicator] incentive will be paid on achieving a contract [sic] rate of 6 per day'. The email went on to state 'A contact is defined as a 'face to face' activity recorded within [the CRM system] or a 'meeting' activity where the customer is listed as 'Attended' in the 'profiled attendees' part of the meeting module within [the CRM system]. Please note that 'non profiled attendees' such as junior doctors are not included in the call rate calculation. All activities must be submitted within [the CRM system] and synchronised (if on the iPad) before midnight on 1st April 2015. Please note all contacts must be made within the ABPI guidelines'. A table at the bottom of the email set out the contact rates for each of the eight neurology sales representatives for the weeks beginning 2 and 9 March along with the average contact rate for each. Three of the eight representatives had an average contact rate at or above the desired 6 contacts/day. The final sentence of the email stated 'Let's make an additional uplift in the last two weeks'.

The second email dated 2 May 2015, subject: '2015 – Rebif- Global Winning Team!' was from a senior director and stated, *inter alia*, that 'To drive new patient share we need to do the following: - Deliver more calls, Call on the right customers and Have impact in call and challenge our customers. Please can you do the following 3 actions, Focus on driving your call volume/contact volume. We really need achieve [sic] 6 calls per day on prescribing customers…' The penultimate paragraph stated, *inter alia*, 'SHOUT OUT THE MESSAGES & challenge your customers while making these additional calls'.

The Panel noted Merck Serono's submission that over a short period of time there had been a significant change to the UK MS therapy environment as several newly licensed MS medicines had become available. This had negatively impacted the sales of Merck Serono's MS medicine Rebif, which had been a leading product for over a decade. Merck Serono commissioned some market research; an on line survey of 30 MS specialists, carried out in January, February and March 2015. The data for January showed customers were being called on more frequently by competitors. Merck Serono further submitted there had been a significant downward trend in the performance of the sales team as measured by the average 'contact' rates. Merck Serono responded to this with various sales and marketing activities and changes to the neurology head office team. A new sales campaign was developed; to help deliver this the sales team were offered a time-limited incentive from 1 – 31 March 2015 inclusive of 30% of key performance indicators (KPIs) which would be paid on achieving a contact rate of 6 per day. Merck Serono submitted that this had a positive effect on the sales team's average daily contact rate recorded at 2.2 in January 2015, 4.5 in February 2015 and 5 in March (Merck Serono's response dated 22 May). Merck Serono submitted that this illustrated that the incentive scheme was a short term measure and had achieved its objective. The Panel noted the average daily contact rate was 4.5 in February and queried how this therefore demonstrated the success of the stated short term incentive in March. The Panel noted that according to the company's response to the Panel's request for further information dated 16 June the monthly daily contact rate with all neurology customers was 2.9 (November 2014), 2.5 (December 2014), 2.4 (January 2015), 4.6 (February 2015), 5.2 (March 2015). The corresponding call rates were 1.8, 1.5, 1.5, 3.2 and 3.6 from November 2014 through to March 2015.

The Panel noted Merck Serono's submission of a letter sent to the KAMs outlining the 2015 incentive plan dated 31 January 2015. This pre-dated the short term incentive implemented for March and stated, *inter alia*, that 25% bonus would be paid on achieving quarterly KPIs. The March incentive stated that 30% bonus would be paid on achieving the KPIs.

The Panel noted that an incentive scheme was generally understood to be, amongst other things, a scheme which *encouraged* increased productivity; it was therefore not a mandatory requirement. Merck Serono had submitted several emails from a senior manager to certain members of the sales team sent on 30 April 2015, which included, *inter alia*, the following statements: 'Please can you let me know your plan to return activity to the required standard, I'd like to see improvements each week until 6 is achieved and please see that your activity levels are raised appropriately and urgently'. It was of concern that contrary to Merck Serono's submission that the incentive scheme ran during March 2015, the aforementioned emails showed that, at the very least, it had continued throughout April and KAMs were expected to continue to achieve a contact rate of 6 per day thereafter. The emails linked the contact rate of 6 per day to the team's business objectives for 2015. In the Panel's view, the KAMs had been given the impression that the contact rate of 6 per day applied not only to March 2015 but for the remainder of 2015.

The email from the senior director dated 2 May had not been certified and stated, *inter alia*, 'We really need achieve *[sic.]* **6 calls per day** on prescribing customers' and referred to driving call volume and contact volume. There was no reference to the relevant requirements of the Code. The Panel noted Merck Serono's submission that the language and tone of the email communication of the 2 May would not have been approved by its signatories and would have been amended. No information was provided as to what would have been amended. Merck Serono further submitted that it had collected no additional evidence that the email communication of 2 May had led to any member of the KAM team breaching the Code in relation to their activities with HCPs. The Panel noted Merck Serono did not appear to have provided any retraction or amendment of this email to the KAM team even though it had submitted that it would have been amended. The Panel was concerned that the email

from the compliance department dated 11 May 2015 reminding staff that all representatives' briefings must be certified was sent after Merck Serono had been notified of this complaint on 7 May.

The Panel noted Merck Serono's submission that it was for each representative, as an experienced KAM to ensure that their chosen activities remained compliant the Code and generally in line with the training they received. The Panel noted the email submitted by the complainant dated 20 March included the statement 'Please note all contacts must be made within the ABPI guidelines', a customer target spreadsheet which had also been included as an appendix, though not directly referred to in Merck Serono's response, reminded the representatives that 'Frequency of contacts to be decided by the activities on the target segment and must be reasonable, however no more than 3 unsolicited calls per customer in line with ABPI code. For the avoidance of doubt, please see Clause 15.4 of the code'. No such reminder was included in any of the emails from the senior manager on 30 April or the email from the senior director dated 2 May.

The Panel considered that while Merck Serono had provided various statements and reminders to their representatives that their activity should comply with the requirements of Clause 15.4, companies had a responsibility to ensure any requirements made of employees were reasonable, achievable and such that employees would not be put in a position that achieving company requirements would mean they might potentially breach the Code. The supplementary information to Clause 15.4 stated, *inter alia*, that 'Targets must be realistic and not such that representatives breach the Code in order to meet them'. Further Clause 15.10 stated 'Companies are responsible for the activities of their representatives if these are within the scope if their employment even if they are acting contrary to the instructions they have been given'.

The Panel considered that the KAMs appeared to have been given little comprehensive and consistent guidance on how to achieve 6 contacts/day and comply with the Code. This was a significant omission. The Panel was concerned that the terminology used in the emails about contacts and calls which was sent to certain KAMs on 30 April from the senior manager and senior director was inconsistent. It was of concern that in response to a specific request the company had been unable to provide its definition of call and contact rates and associated representatives' briefing. The supplementary information to Clause 15.4 required companies when briefing representatives to clearly distinguish between expected call and contact rates. Solicited calls were only described in the briefing to KAMs on how to enter their contact rate in the CRM system. The Panel noted the company's submission that it was able to distinguish between call and contact rates on the CRM system but noted that such ability did not alter the fact that the KAMs had not been adequately advised in this regard.

The Panel noted the neurology sales team currently consisted of 8 KAMs each of which had approximately 50-60 MS specialists in each territory. March 2015 had 22 working days, if a KAM was to achieve the 6 contacts a day this would give an overall contact volume of 132 contacts for that month, which would mean each specialist in each territory would need to be seen on average 2–3 times in the month. The supplementary information to Clause 15.4 stated, *inter alia*, that 'the number of calls made on a doctor or other prescriber and the intervals between successive visits are relevant to the determination of frequency. Companies should arrange that intervals between visits do not cause inconvenience'.

The Panel noted its comments above. The Panel noted that the March incentive scheme was, in reality, a requirement. The Panel considered that achieving this would mean that on the balance of probabilities the representatives would breach the Code in that, in the absence of consistent terminology and briefing on how to achieve 6 contacts/day and remain compliant with the Code, the frequency of representatives' calls would cause inconvenience. On the balance of the evidence a breach of Clause 15.4 was ruled. The Panel noted the requirements of Clause 15.2 which stated, *inter alia*, that 'Representatives must at all times maintain a high standard of ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code'. The Panel noted the ruling above and on balance ruled a breach of Clause 15.2.

The Panel considered Merck Serono's submission that it was its policy and practice that all representatives' briefing material was reviewed and certified according the requirements of the Code, a copy of the relevant standard operating procedure was provided, however the briefing material sent by a senior director in March 2015 and submitted by the complainant had been sent to the representatives before certification. The Panel noted the email from the compliance department had been sent on 11 May. The Panel further noted in a subsequent submission by Merck Serono that the email dated 2 May 2015 headed 'Rebif Global Winning Team!' and provided by the complainant had not been certified. This was disappointing. The Panel noted its comments above regarding the date of the email from the compliance department about the need to certify all representatives' briefing material. A breach of Clause 15.9 was ruled.

Complaint received **7 May 2015**

Case completed **24 July 2015**

CASE AUTH/2758/5/15

GALEN v STIRLING ANGLIAN

Promotion of CosmoCol

Galen submitted a complaint about the promotion of CosmoCol (Macrogol 3350 plus electrolytes) by Stirling Anglian Pharmaceuticals.

An advertisement in MIMS, March 2015 was headed 'CosmoCol Macrogol 3350. Powder for oral solution' and featured pack shots of the CosmoCol range above details of their pack size and cost.

Galen alleged that the abbreviated advertisement was a breach of the Code as it contained details of pack sizes and cost. In addition, stating 'macrogol 3350. Powder for oral solution' did not meet the requirements for providing the non-proprietary name or the active ingredients of Cosmocol. The full non-proprietary name should read 'macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride'.

Galen alleged a further breach of the Code as a leavepiece did not include the non-proprietary name or the active ingredients.

The detailed response from Stirling Anglian is given below.

The Panel noted Stirling Anglian's submission that the reason for recommending CosmoCol was related to its value proposition in terms of cost and pack size. The Panel considered that the content of the advertisement went beyond that described in the Code for an abbreviated advertisement. In the Panel's view the advertisement should have included prescribing information and a breach of the Code was ruled.

The Panel noted that according to its SPC the name of one of the products in the range was CosmoCol Orange Lemon and Lime flavour powder for oral solution. Its active ingredients were given as Macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. The Panel considered that neither the abbreviated advertisement nor the leavepiece listed the active ingredients as reflected in the SPC and breaches of the Code were ruled.

Galen submitted a complaint about an advertisement and a leavepiece for CosmoCol (Macrogol 3350 plus electrolytes) issued by Stirling Anglian Pharmaceuticals. CosmoCol was indicated for the treatment of chronic constipation and faecal impaction.

The advertisement appeared in MIMS March 2015 and had the same date of preparation as the leavepiece February 2015. The 2015 Code applied other than newly introduced requirements which were covered by the transition period which ran until 30 April 2015. In relation to the complaint being considered, there were no relevant newly introduced requirements covered by the transition period for the introduction of the 2015 Code.

A Abbreviated advertisement

This advertisement (ref 00010010005 1.0) appeared in MIMS, March 2015. The advertisement was headed 'CosmoCol Macrogol 3350. Powder for oral solution' and featured pack shots of the CosmoCol range. Below each of the five packs was, *inter alia*, details of pack size and cost.

COMPLAINT

Galen alleged that the advertisement was in breach of Clause 5.2 in that, via copy and visuals, it contained details of pack sizes and cost. Galen noted that the supplementary information to Clauses 5.4, 5.5, 5.6, 5.7 and 5.8, Permitted Information, specifically listed details of pack size and cost as elements which should not be included in abbreviated advertisements. In addition, Galen noted that Clause 5.4 required that abbreviated advertisements must provide, *inter alia*, the non-proprietary name of the medicine or list of active ingredients using approved names where such exist. Galen did not consider that by simply stating 'macrogol 3350. Powder for oral solution' qualified as listing the non-proprietary name or the active ingredients of Cosmocol. The full non-proprietary name should read 'macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride'.

RESPONSE

Stirling Anglian denied any breach of the Code on the basis that the details of pack size and cost stated in the advertisement met the exemption cited in the supplementary information to Clause 5. Stirling Anglian stated that in its view the reason for recommending CosmoCol in the advertisement was directly related to the value proposition in terms of cost and pack size. On that basis the company refuted Galen's alleged breaches of the Code.

In relation to the non-proprietary name, Stirling Anglian stated that it had elected to use the form of words approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) as a description of CosmoCol when a licence authorization was granted which was 'Macrogol 3350 powder for oral solution'. The company thus denied a breach of the Code. However, it had taken the opportunity, following a recent price reduction for CosmoCol to review and modify its promotional material such that CosmoCol was described as follows: 'CosmoCol – Macrogol 3350, sodium chloride, potassium chloride, sodium hydrogen carbonate'. Copies of the revised materials were provided.

In response to a request for further information including confirmation of the non-proprietary name

of CosmoCol, Stirling Anglian provided copies of correspondence from the MHRA regarding the grant of the marketing authorisation for CosmoCol.

The company stated that in each case the name of the medicine was listed as CosmoCol (flavour) powder for oral solution. The name of the medicine was specified in Section 1 of the summary of product characteristics (SPC) and the active ingredients in Section 2.

PANEL RULING

The Panel noted the requirements of Clause 5 and in particular Clause 5.8 which stated that abbreviated advertisements may contain a concise statement consistent with the summary of product characteristics (SPC) giving the reason why the medicine was recommended for the indication or indications given. The Panel noted that the supplementary information to Clauses 5.4, 5.5, 5.6, 5.7, 5.8 and 5.9, Permitted Information, stated that the contents of abbreviated advertisements were restricted as set out in the aforementioned clauses and the following information should therefore not be included in abbreviated advertisements: dosage particulars, details of pack sizes and cost. There might be exceptions to the above if the information provided, for example the cost of the medicine or the frequency of its dosage or its availability as a patient pack, was given as the reason why the medicine was recommended for the indication or indications referred to in the advertisement. Artwork used in abbreviated advertisements must not convey any information about a medicine additional to that permitted under Clauses 5.4, 5.5, 5.6, 5.7, 5.8 and 5.9.

The Panel noted that the advertisement headed 'Family Values' depicted five patient packs beneath each of which was a description of the number of sachets per pack and their cost. Also included were cost claims such as 'lowest cost' and claims about taste and a claim about dosage –'highly versatile half-dose'. The lower half of the advertisement discussed the benefits of the breadth of the CosmoCol range and included comments about the company's qualities under the headings 'Reliable', 'Honest', 'Hardworking', and 'Nurturing'.

The Panel noted the company's explanation that the reason for recommending CosmoCol was related to its value proposition in terms of cost and pack size. The Panel noted the content of the advertisement and considered that the detailed information provided went beyond that described in the relevant supplementary information to Clause 5, set out above and in addition went beyond the provision of a concise statement giving the reason why the medicine was recommended for the indication/ indications given as set out in Clause 5.8. In the Panel's view the detail provided was such that the material could not take the benefit of the exemption for abbreviated advertisements and the need for prescribing information as set out in Clause 5.1. In the Panel's view the advertisement should have included prescribing information as required by Clause 4.1. A breach of Clause 5.2 was ruled.

The Panel noted that Clause 5.4 required abbreviated advertisements to contain, *inter alia*, the non-proprietary name of the medicine or a list of active ingredients using approved names where such existed. The Panel noted that according to its SPC the name of one of the products in the range was CosmoCol Orange Lemon and Lime flavour powder for oral solution. Its active ingredients were given as Macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. The correspondence from the MHRA provided by Stirling Anglian referred to the name of the product as CosmoCol Orange Lemon and Lime flavour powder for oral solution. The Panel considered that as the abbreviated advertisement did not list the active ingredients as reflected in the SPC it did not satisfy the relevant requirement in Clause 5.4 and a breach of that clause was ruled.

B Leavepiece

The leavepiece (ref 00010010006 1.0) at issue was similar in design to the abbreviated advertisement at point A above and had the same heading 'CosmoCol Macrogol 3350. Powder for oral solution'. The date of preparation was February 2015.

COMPLAINT

Galen alleged a breach of Clause 4.3 in that it did not consider Macrogol 3350. Powder for oral solution' listed the non-proprietary name or the active ingredients for CosmoCol. In its view the full non-proprietary name should read 'Macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride'.

RESPONSE

Stirling Anglian noted that it had elected to use the form of words approved by the MHRA as a description of CosmoCol when a licence authorization was granted which was 'Macrogol 3350 powder for oral solution'. The company thus denied a breach of the Code. However, it had taken the opportunity, following a recent price reduction for CosmoCol to review and modify its promotional material such that CosmoCol was described as follows: 'CosmoCol – Macrogol 3350, sodium chloride, potassium chloride, sodium hydrogen carbonate'. Copies of the revised materials were provided.

In response to a request for further information including confirmation of the non-proprietary name of CosmoCol, Stirling Anglian provided copies of correspondence from the MHRA regarding the grant of the marketing authorisation for CosmoCol.

The company stated that in each case the name of the medicine was listed as CosmoCol (flavour) powder for oral solution. The name of the medicine was specified in Section 1 of the summary of product characteristics (SPC) and the active ingredients in Section 2.

PANEL RULING

The Panel noted that the content of the one page leavepiece was closely similar to the advertisement. It was headed 'CosmoCol Macrogol 3350. Powder for oral solution'. The Panel noted that Clause 4.3 required the non-proprietary name or the list of active ingredients using approved names where such existed to appear immediately adjacent to the most prominent display of the brand name.

The Panel noted that according to its SPC the name of one of the products in the range was CosmoCol Orange Lemon and Lime flavour powder for oral solution. Its active ingredients were given as Macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. The correspondence from the MHRA referred to the name of the product as CosmoCol Orange Lemon and Lime flavour powder for oral solution.

The Panel considered that as the leavepiece did not list the active ingredients as reflected in the SPC, the material did not satisfy the relevant requirement in Clause 4.3 and thus a breach of that clause was ruled.

Complaint received **12 May 2015**

Case completed **12 August 2015**

HEAD OF MEDICINES MANAGEMENT v PFIZER

Gabapentin Patient Alert

A medicines management pharmacist complained about a gabapentin patient alert issued by Pfizer. Gabapentin was available generically and marketed by Pfizer as Neurontin. Pfizer also marketed Lyrica (pregabalin). Both Neurontin and Lyrica were indicated for use in neuropathic pain and in epilepsy.

The complainant noted the alert which read, 'Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. *Supported by Pfizer.*'. The alert was activated on some community pharmacy 'Patient Medication Records' (PMR) systems when gabapentin was entered into the system.

The complainant alleged that this activity was disguised promotion and did not maintain high standards. If the Authority agreed, then the complainant also alleged that the activity brought the industry into disrepute.

The complainant submitted that the most likely alternative to gabapentin was pregabalin. The alert suggested that the alternative medicine would have fewer side effects and a safer prescribing profile. However Public Health England had recently alerted health professionals that both gabapentin and pregabalin could to lead to dependence and that they might be misused or diverted. The complainant stated that implying that pregabalin was likely to be a better alternative could be misleading. In addition, the statement directed pharmacists and patients to an alternative without encouraging them to report adverse events through the Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card system. Thus the complainant alleged that the objective of the alert was promotional rather than patient support.

The detailed response from Pfizer is given below and refers to seven different patient alerts for amitriptyline and gabapentin.

The Panel considered that the provision of high quality patient care was an important aim. However it was concerned that Pfizer considered that pharmacists needed to be given the seven patient alerts to support their discussions with patients. The advice regarding adverse events and what to do if symptoms were not controlled was likely to be relevant for all medicines not just those used to treat neuropathic pain. The Panel noted that the patient alerts which referred to adverse events did not remind pharmacists to report them. The Panel also noted that the patient alerts appeared irrespective of whether amitriptyline or gabapentin had been prescribed for neuropathic pain or something else. The patient alerts appeared on the dispensing terminal and not on the patient medication records.

The Panel noted Pfizer's submission that the National Institute for Health and Care Excellence (NICE) recognised that there was considerable variation in how medicines for neuropathic pain were initiated, the dosages used and the order in which they were introduced. NICE noted that for the treatment of all neuropathic pain (except trigeminal neuralgia), initial treatment should be a choice of amitriptyline, duloxetine, gabapentin or pregabalin. If initial treatment was not effective/not tolerated, then one of the three remaining medicines should be offered with subsequent switches being considered if the second or third medicines tried were also not effective/not tolerated. Pfizer marketed two of the four medicines recommended for initial treatment.

The Panel noted that gabapentin and amitriptyline were the most commonly used first-line treatments for phantom limb pain or painful diabetic neuropathy (Hall *et al* 2013). Pfizer submitted that 61% of gabapentin prescriptions were for pain and that pregabalin was much less frequently prescribed. The Panel noted that given the NICE treatment guidelines, if a patient had initially been unsuccessfully treated with amitriptyline, then two of the other three medicines which should be tried were Pfizer's (gabapentin and pregabalin). However given that amitriptyline and gabapentin were the two most widely prescribed medicines for neuropathic pain, a patient who had failed initially with amitriptyline was likely to be switched to gabapentin and *vice versa*.

The Panel noted that although the seven patient alerts were to be used in rotation, triggered by prescriptions for gabapentin or amitriptyline, the complainant had complained about the one which read: 'Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. *Supported by Pfizer.*' The Panel noted the NICE guidelines and that a patient who failed on gabapentin would not necessarily be switched to pregabalin, there were two additional medicines the patient could try depending where they were on the treatment pathway. Although a switch to pregabalin was possible, the Panel did not have evidence before it to show that, as suggested by the complainant, it was the most likely alternative. The Panel noted Pfizer's submission that health professionals did not differentiate pregabalin from gabapentin as their mechanisms of action were similar. The Panel did not consider that the patient alert at issue for gabapentin was disguised promotion for pregabalin as alleged and it ruled no breach. The Panel thus did not consider that the text cited by the complainant implied that pregabalin was likely to be a better alternative to gabapentin or that it suggested that, compared with gabapentin, pregabalin had fewer side effects and a

safer prescribing profile. No breaches of the Code were ruled.

The Panel noted its rulings above and considered that there was no evidence to show that high standards had not been maintained. The Panel did not consider that failing to refer to the reporting of adverse events in the patient alerts in itself meant that high standards had not been maintained. However if it was considered helpful to remind pharmacists about certain elements to support their interactions with patients, then it would have been helpful to also include a reference to the MHRA yellow card scheme. Pfizer had not specifically responded on this point. Nonetheless, the Panel considered that there had been no breaches of the Code including Clause 2.

A head of primary care support and medicines management at a clinical commissioning group (CCG), complained on behalf of that CCG and colleagues from other CCGs, about the activities of Pfizer Limited. The material at issue was a patient alert about gabapentin. Gabapentin was widely available generically and marketed by Pfizer as Neurontin. Pfizer also marketed Lyrica (pregabalin). Both Neurontin and Lyrica were indicated for use in the treatment of epilepsy and neuropathic pain.

COMPLAINT

The complainant stated that the alert was activated on some community pharmacy 'Patient Medication Records' (PMR) systems, triggered when gabapentin was entered into the system..

The patient alert read:

> 'Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. *Supported by Pfizer*.'

The complainant alleged that this activity contravened the Code in relation to disguised promotion, Clause 12.1 that promotional material and activities must not be disguised and Clause 9.1 that high standards of compliance to the Code must be maintained at all times. If the Authority agreed with this, the complainant also alleged a breach of Clause 2, bringing the industry into disrepute.

Clinically, the most likely alternative to gabapentin was another Pfizer medicine, pregabalin, a medicine licensed for use in epilepsy, generalised anxiety disorder and neuropathic pain. The medicines had a very similar structure, acting via the alpha-2-delta subunit of voltage-gated calcium channels.

The alert suggested that the alternative medicine would have fewer side effects and implied a safer prescribing profile. Public Health England had recently alerted health professionals that both gabapentin and pregabalin had the potential to lead to dependence and that they might be misused or diverted.

The complainant stated that implying that pregabalin was likely to be a better alternative could be misleading. In addition, the statement directed pharmacists and patients to an alternative without encouraging/directing them to report their adverse event through the Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card system. Thus the complainant alleged that the alert was a promotional message rather than a supportive statement for patients.

When writing to Pfizer, the Authority asked it to consider the clauses cited by the complainant (2, 9.1 and 12.1) and also Clause 7.2 in relation to the alleged misleading implication that pregabalin was likely to be a better alternative and Clause 7.9 in relation to the alleged suggestion that pregabalin would have fewer side effects and a safer prescribing profile including the comments about dependency and misuse.

RESPONSE

Pfizer submitted that, despite better diagnosis and advances in treatments, the management of neuropathic pain remained very challenging because of the heterogeneity of its aetiologies, symptoms and underlying mechanism. Patients with neuropathic pain could suffer severe pain which could have a significant impact on their quality of life. No single treatment worked in every patient or pain state, and satisfaction with therapy was relatively low in patients with neuropathic pain (Dworkin *et al*, 2010). In randomised clinical trials of medicines for neuropathic pain, many patients did not experience clinically meaningful pain relief and, in addition, frequently experienced burdensome side effects and so might not be able to tolerate their treatment. These results from clinical trials were consistent with several studies of neuropathic pain in the community (Dworkin *et al*).

Pfizer stated that the National Institute for Health and Care Excellence (NICE) Clinical Guideline 173 [Neuropathic pain – pharmacological management] recognised that there was considerable variation in how medicines were initiated, the dosages used and the order in which they were introduced, whether therapeutic doses were achieved and whether there was correct sequencing of therapeutic classes. It was further noted that these factors might lead to inadequate pain control with considerable morbidity. There was a recognition that, 'untreated, pain became entrenched and more difficult to treat. The consequences of long-term pain had a serious impact on both patients and society' (Chief Medical Officer report 2009). A general principle of pain management, as recognised by The British Pain Society/Map of Medicine neuropathic pain guidelines, was the need to reduce delays in optimising pain management for patients.

Pfizer stated that the supplier of the particular PMR system at issue supported patients at the point of dispensing medicines within a pharmacy. The company was committed to improve patients' health and prevent unnecessary suffering by helping patients understand their medicines better. With this aim the supplier supported better adherence to medicines and optimisation of care. The company supported pharmacists and patients and since setting

up it had worked with most of the top 20 life sciences companies in the UK to support approximately 50% of UK pharmacies and 42,000 pharmacies across Europe.

Pfizer submitted that pharmacists routinely gave patient information when they collected their prescription. The PMR supplier was able to provide additional helpful information on the electronic dispensing system to support the discussion with patients. Dispensing the prescribed treatment(s) triggered the information to appear in the electronic dispensing system. The objective of the information was to optimise patient care. The pharmacy intervention was intended to identify patients whose care might not be optimised and to advise them to consult their doctor to see if they might be suitable for alternative treatment options. Alternative treatment options were never named, and could be pharmacological or non-pharmacological.

Given the patient-focussed objectives of the PMR supplier, Pfizer had engaged with it to create information for pharmacists to give to patients whey they dispensed gabapentin and amitriptyline, the most commonly prescribed medicines for neuropathic pain (Hall *et al* 2013).

Given the patient, healthcare and societal challenges as set out above in managing neuropathic pain, the aim of the patient information was to:

- Support pharmacists when they counselled patients to identify if they had experienced inadequate pain relief or side effects from their treatment, and if so to advise the patient to consult their doctor as other treatment options, pharmacological or non-pharmacological, might be suitable for them. The counselling supported patients to make informed choices and manage their condition with support from their health professional.

- Support better management of neuropathic pain in primary care. There was an accepted burden associated with outpatient and pain clinic referrals into secondary care and this could be reduced, where appropriate, with better management of pain in primary care.

The information texts for patients were detailed below, however the complaint specifically related to number 2 (ref NEP0134b). The PMR supplier conducted due diligence with feedback from the PMCPA which twice supported the view that provided the text did not promote a medicine, the information for patients could be regarded as non-promotional. These were certified as non-promotional items (refs NEP0134a/b/c and NEP0227a/b/c/d).

1 Remind your patient that if they are still having pain and/or experience side effects, they should return to their doctor, as alternative treatments are available. Supported by Pfizer Ltd (ref NEP0134a)

2 Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. Supported by Pfizer Ltd (ref NEP0134b)

3 Remind your patient that if they are not getting adequate pain relief whilst taking gabapentin they should return to their doctor, as alternative treatments are available. Supported by Pfizer Ltd (ref NEP0134c)

4 Research shows 38% of people taking amitriptyline for neuropathic pain achieve pain relief. If your patient isn't getting adequate pain relief, advise them to discuss with their doctor as there are other treatments available. Supported by Pfizer Ltd (ref NEP0227a)

5 Inform your patient that some people experience side effects whilst taking amitriptyline. If this is the case, they should discuss with their doctor as alternative treatments are available. Supported by Pfizer (ref NEP0227b)

6 NICE recommends amitriptyline as an initial treatment option for neuropathic pain but many patients may remain in pain. If your patient is still symptomatic, they should speak to their doctor – other treatments are also recommended. Supported by Pfizer (ref NEP0227c)

7 64% of patients on amitriptyline experience at least one adverse event. These may pass; however, if they continue, advise your patients to discuss with their doctor. There are alternatives available. Supported by Pfizer (ref NEP0227d).

The information did not appear on the community pharmacy patient medication records. It appeared on the electronic dispensing system when the medicine was dispensed to enable the information to be provided to the patient by the pharmacist.

Pfizer had not paid for its publication on the patient medication records. The service was not on the patient medication record. It was triggered at the point of dispensing within the dispensing terminal via the PMR desktop application, to enable patient support information to be provided to the patient by the pharmacist. Pfizer had paid for the publication on the dispensing terminal via its desktop application within PMR supplier's pharmacies estate.

Essentially, the alerts prompted the pharmacist to consider the discussion points as part of the counselling normally provided to patients when they received their medicines. There was no additional material provided to the pharmacist.

Pfizer stated that the patient information was certified as non-promotional text and Pfizer ensured that the information did not promote any medicine. Pfizer had been very clear to state that 'alternative treatments were available'. Alternative treatments encompassed a wide number of treatment options, both pharmacological and non-pharmacological (ie pain management programmes, complementary and alternative treatments, exercise, transcutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation, graded motor imagery, cognitive behavioural therapy or supportive psychotherapy, based on the bio-psychosocial model of pain). Indeed, the National Pain Audit showed that 44% of treatment received from NHS pain services was non-

pharmacotherapy (National Pain Audit, 2010-2012). Pfizer therefore did not accept that this information for patients was disguised promotion for pregabalin or any medicine, and as such was not in breach of Clause 12.1.

Pfizer noted the complainant's following points:

- 'Clinically the most likely alternative to gabapentin was another Pfizer medicine, pregabalin'
- 'The alert suggested that the alternative medicine would have fewer side effects and implied a safer prescribing profile'
- 'Public Health England had recently alerted health professionals that both gabapentin and pregabalin had the potential to lead to dependence and that they might be misused or diverted'.
- 'Implying that pregabalin was likely to be a better alternative could be misleading'.

Pfizer disagreed that 'alternative treatments' most likely implied pregabalin and referred to its comments above regarding the wide number of treatment options, both pharmacological and non-pharmacological encompassed in 'alternative treatments'.

There was no suggestion that patients would have fewer side effects or do better with any other options. The text simply advised patients to see their doctor if they experienced side effects as alternative treatment options might be suitable for them. The British Pain Society/Map of Medicine neuropathic pain guidelines highlighted the holistic management of neuropathic pain (pharmacological and/or non-pharmacological) delivered in non-specialist care, and the need for optimal pain management. Many patients had to try many options, both pharmacological and non-pharmacological, before they found a suitable option. This would be in line with standard clinical practice. As there were no promotional claims in this patient information Pfizer denied breaching Clauses 7.2 or 7.9.

Pfizer submitted the programme had undergone due diligence within the company; it had involved medical, legal and compliance colleagues. Pfizer again noted that advice about this type of programme had been sought from the PMCPA. The feedback supported Pfizer's assessment that this was a non-promotional programme which provided information to patients to support their care. Pfizer ensured that there was no promotion or disguised promotion of any medicines. Pfizer was dedicated and committed to maintaining the highest standards of compliance and it believed that high standards had been maintained at all times throughout this patient information programme. Pfizer did not accept that the patient information provided breached Clause 9.1.

Pfizer submitted that as the patient information provided did not represent disguised promotion of pregabalin or any medicine and that high standards of compliance had been maintained at all times, it denied that it had brought the industry into disrepute or breached Clause 2.

In summary, Pfizer reiterated that pharmacological management of neuropathic pain was recognised as challenging. Many patients did not achieve clinically meaningful pain relief and, in addition, might experience burdensome side effects and so were often unable to continue their treatment.

The programme's objective was to optimise the care of patients with neuropathic pain by providing information for them to be delivered by pharmacists at the point of dispensing. This supported the pharmacist when he/she counselled patients to identify if they had experienced inadequate pain relief or side effects and if so, to advise the patient to consult their doctor. Alternative treatment options could include other pharmacotherapies and/or a wide choice of non-pharmacotherapies which were commonplace in pain management. There was no disguised promotion of pregabalin or any medicine or therapy. There were no promotional claims or comparisons and high standards had been maintained throughout. Pfizer thus did not accept that the patient information text breached Clauses 12.1, 7.2, 7.9, 9.1 or 2.

In response to a request for further information, Pfizer submitted that although gabapentin 900-3,600mg/day was licensed for both peripheral neuropathic pain and epilepsy, the vast majority of its use was in pain (61% pain, 1% epilepsy, 39% other) (Ref IMS). Pfizer reiterated that patients were not always optimally treated for neuropathic pain and the aim of the programme was to help address this. The company had focused on gabapentin and amitriptyline as these were the most commonly used treatments for neuropathic pain.

Pfizer noted that the alerts were triggered by the medicine being presented, irrespective of indication. As UK prescriptions did not include the indication, the computer system would not be able to identify what the prescription was for.

Pfizer stated that it did not have the data to show what proportion of patients with peripheral neuropathic pain were likely to be switched to pregabalin if they could not tolerate gabapentin. However, from experience, many health professionals did not differentiate pregabalin from gabapentin as their mechanisms of action were similar. Similarly, the company did not have the data to show what proportion of patients with epilepsy were likely to be switched to pregabalin if they could not tolerate gabapentin.

Pfizer noted that the alerts were rotated on a monthly basis such that one month it would be alert 1, the next alert 2 and so on, there was no prioritisation or weighting given to a particular message.

Pfizer submitted that the alerts did not refer to pharmacological and non-pharmacological treatments, because the PMR desktop application only allowed a maximum of 254 characters and spaces in each alert. Thus due to the character limitation 'treatments' was an appropriate term as it encompassed a wide range of treatment options (pharmacological and non-pharmacological).

Pfizer stated that its objective with this programme was to support patient care by helping the pharmacist to engage the patient in dialogue about their treatment. The patient alert was triggered when either gabapentin or amitriptyline were dispensed as these were the two most commonly used treatments for neuropathic pain. The alerts were not triggered when pregabalin or duloxetine were dispensed as these were much less frequently prescribed.

The alerts prompted the pharmacist to discuss the patient's treatment with them in the course of their natural duties. This was non-promotional material hence the adverse events reporting statement required for promotional material was not required. The alert itself was not directed to the patient nor intended to be shown to the patient so 'reporting of side effects' wording for the patient was not included.

Pfizer stated that the above further supported its position that the patient information text was not in breach of the Code.

PANEL RULING

The Panel noted Pfizer's submission that the Authority had been asked for its view on a patient alert programme and that feedback from the Authority had supported the view that the activity was non-promotional. The Panel noted, however, that when the Authority was asked for advice about materials or activities under the Code it could only give informal guidance based upon its interpretation of the Code and, where available, the outcome of past cases. The Authority could not approve such materials or activities and that if a complaint were to be received about a matter upon which advice had been sought, it would have to be considered in the usual way and on its own particular merits.

The Panel considered that the provision of high quality patient care was an important aim. However it was concerned that Pfizer considered that pharmacists appeared to need to be given the information in the seven patient alerts to support their discussions with patients. The advice regarding adverse events and what to do if symptoms were not controlled was likely to be relevant for all medicines not just those used to treat neuropathic pain. The Panel noted that the patient alerts which referred to adverse events did not remind pharmacists of the need to report them. The Panel also noted that the patient alerts would appear irrespective of whether the patient was prescribed amitriptyline or gabapentin for neuropathic pain or some other indication. The patient alerts appeared on the dispensing terminal and not on the patient medication records.

The Panel noted Pfizer's submission that NICE recognised that there was considerable variation in how pharmacological treatment for neuropathic pain was initiated, the dosages used and the order in which medicines were introduced, whether therapeutic doses were achieved and whether there was correct sequencing of therapeutic classes (NICE CG173). The NICE clinical guideline cited noted that for the treatment of all neuropathic pain (except trigeminal neuralgia), initial treatment should be a choice of amitriptyline, duloxetine, gabapentin or pregabalin. If initial treatment was not effective or was not tolerated, then one of the three remaining medicines should be offered with subsequent switches being considered if the second or third medicines tried were also not effective or not tolerated. Pfizer marketed two out of the four medicines recommended for initial treatment.

The Panel noted that gabapentin and amitriptyline were the most commonly used first-line treatments for patients with phantom limb pain or painful diabetic neuropathy (Hall *et al*). Pfizer submitted that 61% of gabapentin prescriptions were for its use in pain and that pregabalin was much less frequently prescribed. The Panel noted that given the treatment guideline from NICE, if a patient had initially been unsuccessfully treated with amitriptyline, then two of the other three medicines which should be tried were Pfizer's (gabapentin and pregabalin). In the Panel's view given that amitriptyline and gabapentin were the two most widely prescribed medicines for neuropathic pain, a patient who had failed on initial treatment with amitriptyline was likely to be switched to gabapentin and vice versa.

The Panel noted that although Pfizer had produced seven patient alerts to be used in rotation, triggered by prescriptions for gabapentin or amitriptyline, the complainant had complained about the one which read: 'Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. Supported by Pfizer.' The Panel noted the NICE treatment guidelines above and that a patient who failed on gabapentin would not necessarily be switched to pregabalin, there were possibly two additional medicines the patient could try depending where they were on the treatment pathway. Although a switch to pregabalin was a possibility the Panel did not have evidence before it to show that, as suggested by the complainant, clinically the most likely alternative to gabapentin was pregabalin. The Panel noted Pfizer's submission that health professionals did not differentiate pregabalin from gabapentin as their mechanisms of action were similar. The Panel did not consider that the patient alert at issue for gabapentin was disguised promotion for pregabalin as alleged and it ruled no breach of Clause 12.1. Given that the Panel did not consider that the patient alert promoted pregabalin, it also did not consider that the text cited by the complainant implied that pregabalin was likely to be a better alternative to gabapentin as alleged. No breach of Clause 7.2 was ruled. Similarly, the Panel did not consider that the patient alert suggested that compared with gabapentin, pregabalin had fewer side effects and a safer prescribing profile. No breach of Clause 7.9 was ruled.

The Panel noted its rulings above and considered that there was no evidence to show that high standards had not been maintained. The Panel did not consider that failing to refer to the reporting of adverse events in the patient alerts in itself meant that high standards had not been maintained. However if it was considered helpful to remind

pharmacists about certain elements to support their interactions with patients, then it would have been helpful to also include a reference to the MHRA yellow card scheme. Pfizer had not specifically responded on this point. Nonetheless, the Panel considered that there had been no breach of Clause 9.1 and ruled accordingly.

Given the rulings above, the Panel ruled no breach of Clause 2 of the Code.

Complaint received **11 June 2015**

Case completed **14 August 2015**

ANONYMOUS, NON-CONTACTABLE PHARMACIST v BOEHRINGER INGELHEIM

Ofev supply programme

An anonymous, non-contactable complainant who described him/herself as a hospital pharmacist raised two concerns about a programme to provide Ofev (nintedanib) free of charge by Boehringer Ingelheim. Ofev was indicated for the treatment of adults with idiopathic pulmonary fibrosis (IPF). The medicine was first authorised in January 2015 but was not yet reimbursable under the NHS.

The complainant's first concern was that surely this was similar to the old days of providing free medicine and then the NHS being charged once the free programme was finished. Secondly the complainant queried, given that the programme was for those who had 'failed' on Esbriet (pirfenidone), what the criteria were for switching from one medicine to another. The complainant stated that he/she had not received a clear answer to either concern.

A medical member of the company saw the complainant and he/she did not believe this was a clinical trial. When the complainant asked about a protocol, none was forthcoming. The complainant did not believe that this was the role of the medical team and was upset that he/she had agreed to take this appointment.

The complainant believed strongly that this type of programme and behaviour was why the pharmaceutical industry was viewed poorly by the wider community.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that every complainant bore the burden of proving his/her complaint on the balance of probabilities. As the complainant in this case had not provided contact details the Panel could not ask him/her for more information. Boehringer Ingelheim had not been able to identify from the information given, the interaction between the complainant and one of its employees that was alleged to have taken place.

The Panel noted that the commercial teams' briefing document provided stated that the Ofev Supply Programme would only be offered to specialist centres which had, *inter alia*, experience of prescribing Ofev via the Individual Patient Supply Programme. The programme addressed unmet clinical need by making Ofev available to those IPF patients for whom no other licensed and reimbursable treatment was available. The programme was led by medical and was not to be raised proactively with customers by the commercial teams. The briefing explained that Ofev could be offered for use in patients unable to take Esbriet and who had a forced vital capacity (FVC) >50%. Arrangements would change when national guidance about the use of Ofev was agreed.

A 'Dear Doctor' letter, appended to the briefing document and intended to be sent to eligible sites, explained the above and clearly stated that Ofev would only be supplied to patients that could not be treated with a licensed and reimbursable alternative and only to those who met certain inclusion criteria of the pivotal registration studies. The Panel noted Boehringer Ingelheim's submission that no promotional material was associated with the supply programme.

The Panel noted that the complainant had stated that the Ofev supply programme was aimed at those who had failed on Esbriet. This was not so; Ofev would only be supplied to those patients who could not take Esbriet. There was no reference in either the briefing document or the 'Dear Doctor' letter to patients who had failed on Esbriet. In that regard the programme could not be a switch programme as alleged and the Panel ruled no breach of the Code.

The Panel considered that there was no evidence before it to show that the programme was such as to offer, supply or promise any gift, pecuniary advantage or benefit to health professionals or any other relevant decision makers, as an inducement to prescribe, supply, administer, recommend, buy or sell Ofev. No breach of the Code was ruled.

The Panel noted that the supply programme was led by the medical team; commercial teams could not raise the matter proactively with customers. There was no associated promotional material. In the Panel's view the programme was non-promotional and thus it could not be disguised promotion. No breach of the Code was ruled. Further, the supply programme could thus not be a promotional activity disguised as a clinical assessment or the like. No breach of the Code was ruled.

The Panel noted its rulings above and considered that there was no evidence to show that Boehringer Ingelheim had not maintained high standards. No breach of the Code was ruled

Given its rulings above, the Panel ruled no breach of Clause 2.

An anonymous, non-contactable complainant who described him/herself as a pharmacist in a major London teaching hospital complained about the provision of Ofev (nintedanib) by Boehringer Ingelheim. Ofev was indicated for the teatment of adults with idiopathic pulmonary fibrosis (IPF). The

medicine was first authorised in January 2015 but was not yet reimbursable under the NHS.

COMPLAINT

The complainant stated that he/she was advised of a programme related to Ofev aimed at those who had failed on another treatment. The complainant was then advised, with enthusiasm, that Boehringer Ingelheim would supply the medicine free of charge. The complainant had two questions, which could not be answered to his/her satisfaction. The complainant stated that surely this was similar to the old days of free medicine given, like samples, and then the NHS being charged once the free programme was finished; he/she received no answer to this apart from a discussion around patient treatment, which he/she believed was his/her domain and not that of a pharmaceutical company. The second related to the fact that the programme was for those who had 'failed' on Esbriet (pirfenidone) marketed by Intermune. When the complainant asked what the criteria were for switching from one medicine to another he/she was met with a complete lack of clarity. Surely this was an issue, and one, which reminded the complainant of 'switching' programmes when he/she was a junior in asthma.

A medical member of the company saw the complainant and he/she did not believe this was a clinical trial. When the complainant asked about a protocol, none was forthcoming. The complainant did not believe on reading the 2015 Code that this was the role of the medical team and was upset that he/she had agreed to take this appointment.

The complainant stated that he/she had read the Code and believed strongly that this type of programme and behaviour was why the pharmaceutical industry was viewed poorly by the wider community.

Boehringer Ingelheim was asked to respond in relation to Clauses 2, 9.1, 12.1, 12.2, 18.1 and 19 of the 2015 Code.

RESPONSE

Boehringer Ingelheim stated that it was unfortunate that the complainant had chosen to remain anonymous as this limited the company's ability to identify the episode which the complainant referred to and subsequently gather further information about the encounter. Accepting this limitation, Boehringer Ingelheim believed the complainant had referred to a confidential discount available to specific IPF treating hospitals.

Boehringer Ingelheim explained that Ofev was granted a marketing authorization by the European Commission in January 2015. It was one of only two licensed therapies for the treatment of IPF, a rare, progressive and debilitating disease which affected less than 1 in 2,000 of the population. IPF was associated with substantial morbidity and a median life-expectancy of approximately two years following diagnosis. Due to timelines laid out by the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC), there was a substantial period of time between the licensing of Ofev and any possible reimbursement for NHS treated patients eg NICE estimated publication of the nintedanib health technology appraisal (HTA) in January 2016, with commissioning of care from NHS England likely to be 90 days after that. Because of either a medical contraindication to Esbriet, or because of national restrictions in the reimbursement of Ofev, there was a cohort of IPF patients who fell within the licensed indications for Ofev who currently could not access any other licensed and reimbursed therapy for their disease.

Boehringer Ingelheim explained that in response to demand from physicians, it provided a confidential discount exclusively to interstitial lung disease (ILD) specialist centres which were already commissioned to treat patients with IPF. The discount was only available to treat patients who were unable to access Esbriet, either because they fell outside of its national reimbursement criteria or because they had a medical contraindication to it. In the event of a national agreement for the reimbursement of Ofev treatment, sites where IPF care was commissioned would no longer be eligible for this discount when they purchased Ofev for patients who now became eligible for reimbursement. All participating sites were aware of this and Boehringer Ingelheim would not retrospectively charge for the supply of Ofev to patients who received treatment by way of this discount prior to the reimbursement decision and had subsequently become eligible for reimbursement. Any site with patients that were not covered by these reimbursement guidelines would continue to receive the agreed discount specifically to treat these patients up until the responsible physician made a clinical decision to stop treatment. This approach was discussed and agreed with NHS England before the discount was provided, with the express agenda of formulating an approach that would not produce additional expense for the NHS, but would benefit these patients where no other licensed and reimbursed alternative was available.

Boehringer Ingelheim stated that given the above complexities, the 'Patient in Need Programme', had been established to ensure consistent and appropriate application of the discount.

The provision of this discount was in response to clinicians' requests and reflected Boehringer Ingelheim's ethical responsibility as the marketing authorization holder for a treatment of such a serious orphan disease. In order to ensure clear differentiation of this ethical provision of a medicine from any inappropriate perception of commercial activity, all proactive communication with ILD centres was through Boehringer Ingelheim's medical team. There was no associated promotional material and the Ofev promotional teams had been briefed not to raise the issue proactively and to reactively direct enquiries to the medical team.

Following an internal review, given that the complainant was anonymous, Boehringer Ingelheim could not identify a member of a medical team who had had a discussion with a London pharmacist in

this context and it thus could not comment further on the complainant's statements regarding his/her perception of the interaction. However, to ensure that the best possible standard with regard to the communication of this programme by Boehringer Ingelheim's promotional and non-promotional field forces was maintained it had, subsequent to receiving this complaint, undertaken further discussion and training with all the relevant individuals.

With regard to Clauses 2 and 9.1, Boehringer Ingelheim stated that the confidential discount provided to sites commissioned to treat IPF was entirely non-promotional with no activities or material associated with promotion of Ofev. All promotional Ofev team members had been briefed to this effect (briefing document provided). The discount scheme was provided by Boehringer Ingelheim to help clinicians manage IPF patients who had no alternative licensed and reimbursed treatment option, to bridge the time between the grant of the marketing authorization and any future reimbursement decisions. Further, Boehringer Ingelheim believed that it had taken appropriate steps to help provide, for ethical reasons, a treatment alternative to those with a debilitating disease that had no other licensed and reimbursed alternative. Boehringer Ingelheim strongly rejected any claim that it had discredited or reduced confidence in the industry, or maintained anything but the highest standards, indeed, it believed the reverse was true. Boehringer Ingelheim considered that failure to offer Ofev to patients in this limited situation, where no licensed and reimbursed alternative was available for such a rare and debilitating disease, prior to the grant of reimbursement approval, would discredit the industry.

With regard to Clause 12.1, Boehringer Ingelheim stated that as noted above, the provision of the discount was non-promotional and as such there was no disguised promotional activity or material.

With regard to Clause 12.2, Boehringer Ingelheim stated that as noted above, the provision of the discount was a non-promotional activity. It was not a market research activity, a clinical assessment, post marketing surveillance or experience programme, or a post-authorization study as referred to in Clause 12.2.

With regard to Clause 18.1, Boehringer Ingelheim stated that it had provided a discount to commercial stock prior to reimbursement as part of its ethical obligation to provide access to patients as the marketing authorization holder in an orphan indication. The discount was only available for patients for whom there was no licensed and reimbursed alternative treatment available, in this specific orphan disease setting, in a non-promotional manner. The alternative to using the provided discount in this situation was to offer no treatment. Boehringer Ingelheim strongly maintained this was not an inducement to prescribe, supply, administer, recommend, buy or sell Ofev.

With regard to Clause 19, Boehringer Ingelheim stated that the discount to commercial stock was not part of any medical or educational goods or service programme. More importantly, provision of the discount was not a switch or therapy review programme. The discount was only available to recognised ILD centres which were commissioned to treat IPF patients, exclusively for patients unable to receive the only other alternative licensed and reimbursed therapy, thus meeting a clear unmet clinical need.

In summary, Boehringer Ingelheim reiterated the following points:

- Due to the anonymity of the complainant, Boehringer Ingelheim was unable to discover the nature of the interaction described, however it believed the complainant had referred to a confidential discount scheme for Ofev.

- The discount for Ofev was only available to sites commissioned to treat IPF patients and was only available for the treatment of those who had no alternative licensed and reimbursed treatment option. It was not a switch programme. Boehringer Ingelheim stressed that if it did not provide this discount to this group of patients, given the current lack of reimbursement for Ofev and the limited treatment options available, these patients would have no alternative licensed and reimbursed treatment option for their serious disease.

- The discount would continue to be applied up until the point that Ofev treatment was commissioned in the treating hospital. Boehringer Ingelheim would not offer the discount to any patients who were, from that point onwards, eligible for reimbursed treatment. There would be no retrospective costs applied for the patients treated under this discount who subsequently become eligible for reimbursed therapy. Any patient offered the discount prior to the publication of reimbursement guidance that was subsequently not eligible for reimbursed nintedanib treatment would continue to receive Ofev at the previously agreed discount until a clinical decision was made to cease treatment.

- Provision of the discount was managed by the medical team in a non-promotional manner. Promotional teams were briefed not to raise the discount proactively and if asked, they were to direct enquiries to the medical team.

- Boehringer Ingelheim believed it had acted with the highest integrity to provide a discount for Ofev at the current time, where it was licensed but not reimbursed, to commissioned prescribing centres, and to IPF patients who had no alternative licensed and reimbursed treatment available. Boehringer Ingelheim did not believe it had acted in breach of Clause 9 and its actions did not bring the industry in to disrepute as described in Clause 2. To the contrary, Boehringer Ingelheim believed that not providing such a discount, to enable availability of Ofev for this limited patient population, would be viewed as withholding treatment for patients with a significant need and no other option.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. Anonymous complaints were accepted and like all complaints, judged on the evidence provided by the parties. The Panel noted that every complainant bore the burden of proving his/her complaint on the balance of probabilities. As the complainant in this case had provided no contact details the Panel could not ask him/her for more information. Boehringer Ingelheim had not been able to identify from the information given, the interaction between the complainant and one of its employees that was alleged to have taken place.

The Panel noted that the supplementary information to Clause 18.1, Patient Access Schemes stated that such schemes were acceptable in principle under the Code provided they were carried out in conformity with its requirements.

The Panel noted that the commercial teams' briefing document provided stated that the Ofev Supply Programme would only be offered to specialist centres which had experience of prescribing Ofev via the Individual Patient Supply Programme and which had signed a new agreement for the Ofev Supply Programme. The programme was designed to address unmet clinical need by making Ofev available to those IPF patients for whom no other licensed and reimbursable treatment was available (Ofev was licensed but currently not reimbursable). The programme was to be led by the medical team and was not to be raised proactively with customers by the commercial teams. The only currently licensed and reimbursable treatment available was Esbriet which was restricted by NICE guidance to use in patients with a forced vital capacity (FVC) of 50-80%. The briefing explained that under the Ofev Supply Programme, Ofev could be offered for use in patients unable to take Esbriet and who had an FVC >50%. The programme would close to new patients when national guidance was agreed but that those already in the programme would continue to receive stock until local reimbursement was agreed. Patients who did not fulfil local reimbursement guidance would continue to receive free stock until they either became eligible for reimbursement or a clinical decision was taken to discontinue their treatment.

A 'Dear Doctor' letter appended to the briefing document and explaining the above was dated to be sent to eligible sites at the beginning of June 2015. The letter clearly stated that Ofev would only be supplied to patients that could not be treated with a licensed and reimbursable alternative and only to those who met the FVC inclusion criteria of the INPULSIS trial programme (the pivotal registration studies). The Panel noted Boehringer Ingelheim's submission that no promotional material was associated with the supply programme.

The Panel noted that the complainant had stated that the Ofev supply programme was aimed at those who had failed on another treatment (Esbriet). This was not so; Ofev would only be supplied under the programme to those patients who could not take Esbriet. There was no reference in either the briefing document or the 'Dear Doctor' letter to patients who had failed on Esbriet. In that regard the programme could not be a switch programme as alleged and the Panel ruled no breach of Clause 19.1.

The Panel noted the complainant's inference that the arrangements were not *bona fide*; that once the 'free programme' had finished the NHS would be charged for the medicine. The Panel noted the arrangements for the scheme as set out above; it considered that there was no evidence before it to show that the programme was such as to offer, supply or promise any gift, pecuniary advantage or benefit to health professionals or any other relevant decision makers, as an inducement to prescribe, supply, administer, recommend, buy or sell Ofev. No breach of Clause 18.1 was ruled.

The complainant appeared to be confused about the role of a member of the medical team at a meeting. As noted above, Boehringer Ingelheim was unable to identify the interaction. The Panel noted that the supply programme was led by the medical team; commercial teams could not raise the matter proactively with customers. There was no associated promotional material. In the Panel's view the programme was non-promotional and thus it could not be disguised promotion. No breach of Clause 12.1 was ruled. Further, the supply programme could thus not be a promotional activity disguised as a clinical assessment or the like. No breach of Clauses 12.2 was ruled.

The Panel noted its rulings above and considered that there was no evidence to show that Boehringer Ingelheim had not maintained high standards. No breach of Clause 9.1 was ruled

Given its rulings above, the Panel ruled no breach of Clause 2.

Complaint received **22 June 2015**

Case completed **15 July 2015**

BRISTOL-MYERS SQUIBB and PFIZER/DIRECTOR v BAYER

Alleged breach of undertaking

Bristol-Myers Squibb and Pfizer complained that a Xarelto (rivaroxaban) leavepiece entitled 'For elderly patients taking aspirin for stroke prevention ... It's time to rethink their protection' breached the undertaking given by Bayer in Case AUTH/2650/11/13.

As the complaint was about an alleged breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The complainants referred to Case AUTH/2650/11/13 which concerned another Xarelto leavepiece and noted the Panel's view that 'although Patel *et al* [2011, the ROCKET AF trial] 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 [gastrointestinal] bleeds vs patients on warfarin; the health professionals could thus manage that risk appropriately'. Bayer was ruled in breach of the Code.

The leavepiece now at issue profiled a patient, a 75 year old woman with non-valvular atrial fibrillation (NVAF) who was currently prescribed aspirin. The material thus unequivocally focussed on the indication of stroke prevention in NVAF.

Bristol-Myers Squibb and Pfizer noted that a page headed 'Xarelto: Demonstrated safety profile across indications' provided the following information about the safety of Xarelto in NVAF:

> **'In patients with non-valvular AF, from the ROCKET-AF trial:**
> - **Xarelto demonstrated a comparable safety profile vs warfarin.'**

Bristol-Myers Squibb and Pfizer stated that following this text there was no further mention of safety information from Patel *et al* (2011). The remainder of the page highlighted bleeding safety data from EINSTEIN which was data from a population with venous thromboembolism (VTE) not NVAF. Importantly, no secondary safety endpoints for bleeding from Patel *et al* had been included. GI bleeding rates for Xarelto compared with warfarin from Patel *et al* had been omitted.

The complainants alleged that the page was misleading as not all key safety endpoints for Xarelto were comparable to warfarin in Patel *et al*. Bristol-Myers Squibb and Pfizer noted that major bleeding from GI sites occurred significantly more frequently in the rivaroxaban group than in the warfarin group; 224 bleeding events (3.2%) vs 154 bleeding events (2.2%) (p<0.001) respectively.

Furthermore Section 4.4 of the Xarelto summary of product characteristics (SPC) highlighted the difference between Xarelto and warfarin with regard to GI bleeding including:

> **'Haemorrhagic risk**
> **… In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long-term rivaroxaban treatment compared with VKA [vitamin K antagonist] treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/ haematocrit could be of value to detect occult bleeding, as judged to be appropriate.'**

Bristol-Myers Squibb and Pfizer alleged that Bayer had failed to comply with the undertaking in Case AUTH/2650/11/13 and was in breach of various clauses of the Code including Clause 2.

The detailed response from Bayer is given below.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted its rulings in Case AUTH/2650/11/13 related to a page 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 safety data from Patel *et al* which compared Xarelto and warfarin. The page featured a bar chart above the claim 'Comparable safety profile vs warfarin with an increased risk of bleeding from GI sites'. The Panel noted 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 had been ruled.

Turning to Case AUTH/2776/7/15, the Panel noted the page at issue was headed 'Because of Jean's age and hypertension she's at moderate risk of a major bleed' followed by 'Xarelto: Demonstrated safety profile across indications' above 'In patients with non-valvular AF, from the ROCKET-AF trial: Xarelto demonstrated a comparable safety profile vs warfarin'. The Panel noted that the claim 'Xarelto demonstrated a comparable safety profile vs warfarin' was referenced to Patel *et al*, rather than the ROCKET AF trial.

The Panel considered that there were differences between the material considered in Case

AUTH/2650/11/13 and that now at issue. The leavepiece at issue broadly compared the safety profile of Xarelto vs warfarin. The claim at issue did not mention specific bleeding sites or the risk of bleeds *per se*. Subsequent claims on the same page did not mention specific bleeding sites although the risk of major and non-major and clinically relevant bleeds were referred to. The material at issue in Case AUTH/2650/11/13 had, *inter alia*, compared certain bleeding events in a bar chart and referred in text below this bar chart to GI bleeding events. The Panel considered the claim now at issue 'In patients with non-valvular AF, from the ROCKET-AF trial: Xarelto demonstrated a comparable safety profile vs warfarin', was not sufficiently similar to that at issue in Case AUTH/2650/11/13 for it to be covered by the undertaking given in that case. Thus the Panel ruled no breach of the Code including Clause 2.

Bristol-Myers Squibb and Pfizer Limited complained, as the Bristol-Myers Squibb and Pfizer Alliance, that promotional material for Xarelto (rivaroxaban) breached the undertaking given by Bayer plc in Case AUTH/2650/11/13. Bristol-Myers Squibb and Pfizer were the complainants in that case.

As the complaint was about an alleged breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Bristol-Myers Squibb and Pfizer now drew attention to a six page, gate-folded leavepiece entitled 'For elderly patients taking aspirin for stroke prevention... It's time to rethink their protection' (reference January 2015 L.GB.12.2014.9154,). The leavepiece introduced a patient profile, Jean, a 75 year old woman with non-valvular atrial fibrillation (NVAF) who was currently prescribed aspirin.

The indications for Eliquis (apixaban) jointly marketed by Bristol-Myers Squibb and Pfizer and Xarelto included the prevention of stroke and systemic embolism in adults with NVAF with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

COMPLAINT

Bristol-Myers Squibb and Pfizer referred to Case AUTH/2650/11/13 which concerned a Xarelto leavepiece (reference L.GB.02.2013.1576c, February 2013). The complainants noted that in that case the Panel's view was 'although Patel *et al* [2011, ROCKET-AF trial] 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 [gastrointestinal] bleeds vs patients on warfarin; the health professionals could thus manage that risk appropriately'. Bayer was ruled in breach of Clauses 7.2 and 9.1.

The complainants stated that in the leavepiece now at issue the patient profile, a woman with NVAF, was referred to on five of the six pages and thus the leavepiece unequivocally focussed on the indication of stroke prevention in NVAF.

Bristol-Myers Squibb and Pfizer drew attention to a page in the leavepiece which referred to the safety profile of Xarelto. The page was headed 'Xarelto: Demonstrated safety profile across indications'. The information provided about the safety of Xarelto in NVAF was:

> 'In patients with non-valvular AF, from the ROCKET-AF trial:
> - Xarelto demonstrated a comparable safety profile vs warfarin'

Bristol-Myers Squibb and Pfizer stated that following this text there was no further mention of safety information from Patel *et al* (2011). Importantly, no secondary safety endpoints for bleeding from Patel *et al* had been included in the material. GI bleeding rates for Xarelto compared with warfarin from Patel *et al* had been omitted.

Bristol-Myers Squibb and Pfizer alleged that the page was misleading as not all key safety endpoints for Xarelto were comparable to warfarin in Patel *et al*. Based on the published paper and supplementary appendix, Bristol-Myers Squibb and Pfizer noted that major bleeding from GI sites occurred significantly more frequently in the rivaroxaban group than in the warfarin group; 224 bleeding events (3.2%) vs 154 bleeding events (2.2%) ($p<0.001$) respectively.

Furthermore the Xarelto summary of product characteristics (SPC) (December 2014), in Section 4.4 Special Warnings and Precautions for use, contained the following text highlighting the difference between Xarelto and warfarin with regard to GI bleeding:

> <u>Haemorrhagic risk</u>
> '…In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long-term rivaroxaban treatment compared with VKA [vitamin K antagonist] treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.'

In summary Bristol-Myers Squibb and Pfizer alleged that Bayer had failed to comply with the undertaking in Case AUTH/2650/11/13. The current material omitted important safety information when informing health professionals about the GI bleeding profile of Xarelto for stroke prevention in NVAF compared with warfarin. Because of the seriousness of this matter the companies alleged breaches of Clauses 2, 7.2, 9.1 and 29.

RESPONSE

Bayer noted that the undertaking from Case AUTH/2650/11/13 related to the leavepiece, 'Anticoagulation: why Xarelto (rivaroxaban) matters', (ref L.GB.02.2013.1576c) and specifically to a bar chart on page 4, as well as the content under the bullet point 'safety profile matters' on page 8 of that leavepiece. The bar chart and bullet point detailed certain safety events from the ROCKET AF trial that were favourable to Xarelto (fatal bleeding,

intracranial bleeding and critical organ bleeding events). However, in the bar chart and on page 4, presentation of unfavourable GI bleeding data was not given equal prominence as the favourable events.

ROCKET AF was a randomised double-blind, double dummy event-driven trial with an objective to demonstrate non-inferiority of Xarelto compared with warfarin in patients with NVAF who had a history of stroke or at least two additional independent risk factors for stroke. 14,264 patients were randomized to either rivaroxaban or warfarin.

The primary efficacy endpoint was the composite of stroke and non-CNS systemic embolism. In the pre-specified per protocol population rivaroxaban was shown to be non-inferior to warfarin while demonstrating superior efficacy in the pre-specified safety as treated analysis.

The primary safety endpoint was the composite of major and clinically relevant non-major bleeding. Rates of major and non-major clinically relevant bleeding were similar in the Xarelto and warfarin groups. There were no differences between Xarelto and warfarin in the individual components of the composite primary safety endpoint. Rates of major bleeding were similar in the Xarelto and warfarin groups (3.6% and 3.4%, respectively; p=0.58). The rates of non-major clinically relevant bleeding were also similar in the Xarelto and warfarin groups (11.8 and 11.4% respectively; p=0.35).

Bayer noted that the present complaint (Case AUTH/2776/7/15) also related to a claim based on ROCKET AF data. The claim at issue was:

> 'In patients with non-valvular AF, from the ROCKET-AF trial:
> • Xarelto demonstrated a comparable safety profile versus warfarin'

Bayer did not agree that the claim failed to comply with the undertaking given in Case AUTH/2650/11/13 as alleged. In the current leavepiece only data relating to the primary safety endpoint was presented. Unlike the leavepiece at issue in Case AUTH/2650/11/13 there was no reference to specific bleeding events.

Bayer stated that in Case AUTH/2650/11/13 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"'

and

> '... 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.'

As a result of the Panel's ruling, Bayer submitted that it undertook to provide comparable data for GI bleeding whenever data for other bleeding events, where there was significant advantage for Xarelto vs warfarin, were presented and that the GI data would always be quantified in the same way.

Bayer stated that in the leavepiece now at issue there were no references to the aforementioned specific favourable bleeding events with Xarelto. Bayer therefore submitted that there had been no breach of undertaking.

Bayer noted that the leavepiece at issue in Case AUTH/2650/11/13 was withdrawn as was all material with a similar presentation of the favourable safety events in question that were not balanced by equal presentation of Xarelto GI bleeding data. In addition, a briefing was drafted and circulated to clarify this, and other undertakings from the case.

In response to a request for further information for specific comments on Clauses 7.2, 9.1, 29 and 2 with respect to the leavepiece now at issue, Bayer stated the complaint was about a breach of undertaking. More specifically, the allegation was that the material in question omitted important safety information when communicating with health professionals regarding the GI bleeding profile with rivaroxaban for stroke prevention in NVAF. The complainants concluded that because of the alleged breach of undertaking, the material was in breach of Clauses 7.2, 9.1, 29 and 2.

Bayer noted that the claim

> 'In patients with non-valvular AF, from the ROCKET-AF Trial
> • Xarelto demonstrated a comparable safety profile vs warfarin'

did not include the GI bleeding profile. Bayer submitted that the justification for this was that there was no reference to other specific bleeding events as already described previously. Bayer submitted that the undertaking from Case AUTH/2650/11/13 was that Bayer agreed to provide comparable data for GI bleeding whenever data for other bleeding events from the ROCKET AF trial (like intracranial haemorrhage retroperitoneal and fatal bleeding, where there were significant advantages for Xarelto vs warfarin) were presented, and that the GI bleeding data would always be presented in the same way.

Consequently Bayer did not accept that there had been a breach of undertaking and therefore of Clauses 29, 7.2, 9.1 or 2.

PANEL RULING

The Panel noted that Bristol-Myers Squibb and Pfizer alleged a breach of the undertaking given in Case AUTH/2650/11/13. The companies also referred to the omission of important safety information when communicating to health professionals regarding the GI bleeding profile of rivaroxaban for stroke prevention in NVAF compared to warfarin and stated that due to the seriousness of this matter the material was also in breach of Clauses 7.2, 9.1 and 2. The Panel

noted that the introductory paragraph to the complaint stated that it concerned a breach of undertaking. The Panel thus considered the complaint solely in relation to the alleged breach of undertaking and Clauses 2, 9.1 and 29.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that Pfizer and Bristol-Myers Squibb alleged that the claim 'In patients with non-valvular AF, from the ROCKET-AF trial: Xarelto demonstrated a comparable safety profile vs warfarin' in the leavepiece now at issue, January 2015 L.GB.12.2014.9154, was such that Bayer had failed to comply with the undertaking given in Case AUTH/2650/11/13.

The Panel noted its rulings in Case AUTH/2650/11/13 related to page 4 of a booklet 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 safety data from Patel *et al* which compared Xarelto and warfarin. The principal 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 GI sites occurred more frequently in the Xarelto group (3.2% vs 2.2%, p<0.001). The page at issue in Case AUTH/2650/11/13 featured a bar chart above the claim 'Comparable safety profile vs warfarin with an increased risk of bleeding from GI sites'. The Panel noted 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 had been ruled.

Turning to the present case, Case AUTH/2776/7/15, the Panel noted the leavepiece was entitled 'For elderly patients taking aspirin for stroke prevention…' with a picture of a middle aged lady on the front 'Jean' who at 75 had been diagnosed with NVAF one month ago. She had a prior medical history of hypertension and mild congestive heart failure.

The page at issue was headed 'Because of Jean's age and hypertension she's at moderate risk of a major bleed' followed by 'Xarelto: Demonstrated safety profile across indications' above 'In patients with non-valvular AF, from the ROCKET AF trial: Xarelto demonstrated a comparable safety profile vs warfarin'. The Panel noted that the claim 'Xarelto demonstrated a comparable safety profile vs warfarin' was referenced to Patel *et al*, rather than the ROCKET AF trial.

The Panel considered that there were differences between the material considered in Case AUTH/2650/11/13 and that now at issue. The Panel considered that the material now at issue broadly compared the safety profile of Xarelto vs warfarin. The claim at issue did not mention specific bleeding sites or the risk of bleeds *per se*. Neither did subsequent claims on the same page mention specific bleeding sites although the risk of major and non-major and clinically relevant bleeds were referred to. The material previously at issue in Case AUTH/2650/11/13 had, *inter alia*, compared certain bleeding events in a bar chart and referred in text below this bar chart to GI bleeding events. The Panel considered the claim in the leavepiece now at issue 'In patients with non-valvular AF, from the ROCKET-AF trial: Xarelto demonstrated a comparable safety profile vs warfarin', was not sufficiently similar to that at issue in Case AUTH/2650/11/13 for it to be covered by the undertaking given in that case. Thus the Panel ruled no breach of Clause 29. Given this ruling the Panel also ruled no breach of Clauses 2 and 9.1.

Complaint received **30 June 2015**

Case completed **19 August 2015**

ANONYMOUS, NON-CONTACTABLE v SANOFI

Representatives' business cards

An anonymous, non-contactable complainant alleged a breach of the Code as business cards used by key account managers (KAMs) at Sanofi featured the brand name of the medicine being promoted. The non-proprietary name was given and there was no prescribing information.

The detailed response from Sanofi is given below.

The Panel noted that the complainant was anonymous and non-contactable. Like all complaints, anonymous complaints were judged on the evidence provided. The complainant bore the burden of proving his/her complaint on the balance of probabilities.

The business card in question carried the company name, the company representative's name and job title 'Clexane Key Account Manager'. The product name was given as part of the job title. It was not in logo format nor were any claims made about the product. Contrary to the complainant's statement, the non-proprietary name was not included. The Panel noted the promotional role of representatives however in the absence of any detailed information about the use of these specific business cards by the representative it did not consider that the item was promotional as alleged.

The Panel did not consider that the requirement to include prescribing information applied. No breach of the Code was ruled.

An anonymous, non-contactable complainant complained about business cards used by key account managers (KAMs) at Sanofi. The two business cards provided by the complainant featured the company name and company logo in the top centre. On the left side of the card was printed a KAM's name under which appeared 'Clexane Key Account Manager'. This was followed below by the KAM's contact details. Clexane (enoxaparin) was indicated for a number of conditions including various thromboembolic disorders.

COMPLAINT

The complainant alleged a breach of the Code as the business cards featured the brand name of the medicine being promoted. The non-proprietary name was given and there was no prescribing information.

When writing to Sanofi, the Authority asked it to respond in relation to Clause 4.1 of the Code.

RESPONSE

Sanofi noted that the complainant referred to the non-proprietary name being stated on the business cards. It was not.

Sanofi stated that it considered that a business card was non-promotional material. Therefore, as directed by Clause 4.1, it did not believe that it required prescribing information. A business card was non-promotional because, as per Clause 1.2, it was 'a factual, accurate, informative announcement'.

Sanofi stated that the purpose of a business card was to identify the representative, contemporaneously or in the future; it provided a health professional with clarity regarding with whom they were speaking. Given that it was non-promotional, it followed that it did not require certification under Clauses 14.1 and 14.3 and therefore Sanofi did not hold a certificate on file.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. Like all complaints, anonymous complaints were judged on the evidence provided. The complainant bore the burden of proving his/her complaint on the balance of probabilities.

The business card in question carried the company name, the company representative's name and job title 'Clexane Key Account Manager'. The product name was given as part of the job title. It was not in logo format nor were any claims made about the product. Contrary to the complainant's statement, the non-proprietary name was not included. The Panel noted the promotional role of representatives however in the absence of any detailed information about the use of these specific business cards by the representative it did not consider that the item was promotional as alleged.

The Panel did not consider that the requirement to include prescribing information applied. No breach of Clause 4.1 was ruled.

Complaint received **3 July 2015**

Case completed **22 July 2015**

CASE AUTH/2778/8/15

MERZ v IPSEN

Promotion of Dysport

Merz complained about two leavepieces for Dysport (a botulinum toxin type A (BoNT-A) product) issued by Ipsen. The leavepieces detailed dose ratios for Dysport vs other BoNT-A medicines (including Merz's product Xeomin); one leavepiece was based on dosing data from summaries of product characteristics (SPCs), and the other on a systematic review of published clinical studies.

Merz was concerned that Ipsen appeared to wish to claim that there was an unpredictable dose-response relationship (dose ratio) between the different BoNT-A medicines on the market. Ipsen explained that the two leavepieces were part of a campaign to dispel the myth that a blanket, single dose ratio could be applied across all indications. The detailed response from Ipsen is given below.

With regard to the leavepiece based on data from the SPCs, Merz stated that regulatory studies often used different endpoints and so data derived from them was not suitable for an indirect comparison. Further, to indirectly derive dose ratios from SPC data was unacceptable and misleading.

The Panel considered that the leavepiece at issue clearly compared the dosage information taken from the SPCs for Dysport, Botox and Xeomin. Although SPC doses were derived from registration studies, the Panel did not consider that the leavepiece was a comparison of these studies *per se* as alleged. In that regard no breach of the Code was ruled. The Panel noted that the aim of the leavepiece was to counter a claim that a single dose ratio could be applied across the board when changing patients from Dysport to another BoNT-A. In terms of recommended initial doses of shared indications for Dysport and Xeomin only one dose ratio was stated ie 1.6:1 for the treatment of blepharospasm. In terms of maximum doses for the two medicines dose ratios of 3.3:1 and 2.4:1 were given for cervical dystonia and for blepharospasm respectively. This countered a single blanket dose ratio switch. Nonetheless, in the Panel's view, the leavepiece appeared to give unequivocal, recommended Dysport:other BoNT-A dose ratios for each indication listed. In the Panel's view this was misleading as each dose ratio given was based on an indirect comparison of SPC doses for Dysport and the other medicine, not on a head-to-head clinical study of the two; the claims could not be substantiated. Breaches of the Code were ruled.

Merz further alleged that the dose ratios based on the maximum doses of the BoNT-A medicines ignored potential consequences of switching and did not encourage the rational use of medicines. Merz noted a dose ratio of 3.3:1 (Dysport: Xeomin) had been presented for cervical dystonia. This meant that if a patient was receiving 750-1000 units of Dysport (recommended range 250-1000 units; the SPC stated that higher doses were associated with an increase in side-effects), they would require 227-300 units of Xeomin – well about the normal recommended maximum dose of 200 units (although the SPC stated that up to 300 units might be given).

The Panel noted that the leavepiece stated, without explanation, that the recommended maximum dose of Xeomin for cervical dsytonia was 300 units. The maximum recommended dose for Dysport in the treatment of cervical dystonia was simply stated to be 1000 units and the resultant dose ratio for Dysport:Xeomin at the maximum dose of each was stated to be 3.3:1. Overall the Panel considered that the references to the maximum doses of Dysport and Xeomin in the leavepiece did not accurately reflect the information given in the SPC or alert the reader that more details, particularly about side effects, should be sought. In that regard, and contrary to Ipsen's submission, the Panel did not consider that the statement at the top of the table that the products' SPCs should be consulted for full prescribing information was sufficient. In the Panel's view, the simplistic way in which the information had been presented did not encourage the rational use of the medicines. A breach of the Code was ruled.

Merz noted that the leavepiece based on data from a systematic review of published studies was incomplete in that at least two studies which involved Dysport and Xeomin had not been included.

The Panel noted that the leavepiece (dated January 2014) detailed a meta-analysis conducted in February 2012; it had not been updated to reflect a subsequent meta-analysis conducted in September 2014 and nor did it include data on Dysport:Xeomin which had since been published. The front page of the leavepiece clearly stated that 'no studies compared Dysport and Xeomin'. In so much as it did not detail the 2014 meta-analysis (even assuming that the recently published Dysport: Xeomin studies did not meet the eligibility criteria) the Panel considered that the leavepiece was not based on an up-to-date evaluation of all the data. In the Panel's view, readers would assume that all of the relevant data had been included which was not so. Breaches of the Code were ruled.

Merz alleged that if the two leavepieces were used together, questions posed in the one based on clinical data eg 'Does a single dose ratio exist?' would appear to be answered by the comparison of the SPC doses in the other. Further breaches of the Code were alleged.

The Panel considered that the two leavepieces were inextricably linked and that its rulings above about the leavepiece based on SPC data applied to their combined use.

Merz Pharma UK Limited complained about the promotion of Dysport (a botulinum toxin type A (BoNT-A) product) by Ipsen Limited. The materials at issue were two leavepieces which detailed dose ratios for Dysport compared with other BoNT-A medicines (Allergan's Botox and Merz's Xeomin). The first leavepiece (ref UK/DYS08687(1)), based on data from summaries of product characteristics (SPCs), was headed 'Comparison of SPC Doses' and subheaded 'Ratios derived from SPC doses highlight the variation across indications'. The second leavepiece (ref UK/DYS08686(1)) was entitled 'Botulinum Toxins – The Ratio Challenge' and referred to a systematic review conducted by a life sciences consultancy in February 2012 which calculated dose ratios based on relevant published clinical studies.

Background to the complaint

Merz explained that following feedback from the field and a teleconference with Ipsen it appeared that Ipsen wished to claim that there was a non-linear, or in some way unpredictable, dose-response relationship (dose ratio) between the different BoNT-A products on the market. The consequence of this proposition was that it would not be possible to satisfactorily change patients from one BoNT-A product to another. Merz believed that this position was derived from a commercial defence strategy to slow erosion of Ipsen's market share in the BoNT-A therapeutic market.

To develop this argument Ipsen had manufactured a table of dose ratios from the extrapolation of data which was fundamentally not suitable for comparison. Further, it had failed to balance these data through the deliberate exclusion of recently published, appropriate, well designed comparative and switch studies which contradicted this story. Merz thus considered that the leavepieces provided an incomplete analysis of the data, and a deliberate failure to represent publications which conflicted with Ipsen's message. Merz was concerned that these actions were fundamentally misleading, did not encourage the rational use of medicines and were not in the interests of patient safety.

By way of background, and with regard to the context of the two leavepieces in question, Ipsen submitted that it produced three leavepieces, 'Comparison of SPC Doses' (Point 1 below), 'Botulinium toxins – The Ratio Challenge' (Point 2 below) and 'Considerations for Pharmacists' (not at issue in this complaint) which together constituted the 'Dispelling the Myth' campaign launched in April 2013. The objective of the three leavepieces was to dispel the myth that a single dose ratio could be replicated across all the indications and across an entire health economy with different injectors. Ipsen recognised the challenges health economies faced in managing services and budgets; they were being presented with tender propositions recommending a blanket switch from Dysport at a 4:1 dose ratio which proposed significant cost savings to medicine budgets. Ipsen was anecdotally aware that where clinics or health economies applied such a switch strategy, patients required further titration which resulted in a 4:1 ratio not being met, and therefore cost savings could not be realised.

The SPCs for all the botulinum toxin products were very clear that dosage units were not interchangeable from one product to another and Ipsen deemed it irresponsible to recommend a blanket counter ratio. Ipsen's approach was to educate not only payors (who were not wholly familiar with botulinum toxins), but also clinicians and pharmacists on why cost savings could not be guaranteed based on a single ratio.

The campaign aimed to demonstrate that a single dose ratio could not be applied or replicated across different indications, different patient populations and different injectors with different injection techniques. The two leavepieces in question supported the aim of the campaign by highlighting and demonstrating the variation in dose with regard to the regulatory approved SPC dosages for the three BoNT-A products on the market and the publications on dose ratios. Furthermore Ipsen submitted that the intention of the leavepieces was in line with the ruling in Case AUTH/23870/1/11 (Merz v Allergan) which stated that 'the claim that no set dosing ratio has been established is a not unreasonable reflection of the totality of the evidence and that this claim is not misleading and is capable of substantiation'. Ipsen submitted that its aim with the two leavepieces was to reinforce this message to prescribers ie that the dosing units for the different botulinum toxins were not interchangeable and that there was no set dosing ratio between the different toxins; the two themes, of course, were entirely related.

Ipsen stated that it very clearly briefed both leavepieces to the sales team and spent significant time training the team on how to use the materials appropriately. The briefing presentation used at the mid-cycle meeting in April 2013 was provided.

Ipsen stated that Merz appeared not to have conducted the process to date within the spirit of, and to the letter of, the Code. Merz failed to inform Ipsen when it complained to the PMCPA. In addition a non-linear dose-response, as mentioned by Merz was different to a dose ratio and this terminology was not used or referred to during inter-company dialogue. Ipsen did not use this terminology and was unclear as to why Merz had alleged that it had conveyed such a message.

During the inter-company teleconference, Ipsen explained the intention of the leavepieces in question and asked Merz for constructive input into what it would like to see changed. Merz did not offer any suggestions at this stage. Ipsen however clarified, and gained acceptance from Merz, that if 'technical breaches' of the Code were ruled, it would not impact the fundamental message conveyed by the leavepieces which was that a single dose ratio

could not be applied across different indications and health economies. Ipsen stated that it took its responsibilities under the Code very seriously and was frustrated that it was unable to conclude inter-company dialogue with some positive outcome, as Merz accepted that the message would be unaffected by the outcome of a complaint.

A 'Comparison of SPC Doses' leavepiece

This leavepiece set out the various indications for botulinum toxin treatment and tabulated the SPC doses for Dysport, Botox and Xeomin. The last column of the table was headed 'Dose ratios' and where relevant the dose ratios were given for, *inter alia*, Dysport:Xeomin.

1 Misleading extrapolation of data from the SPC

COMPLAINT

Merz submitted that regulatory studies designed for the approval of a product often compared the product under evaluation with another already marketed product, such as in the case of Xeomin for the indication of cervical dystonia which was compared with Botox. Alternatively, for emerging indications products were often compared to the existing standard of care plus placebo, as in the case of the upper limb spasticity licence for Dysport. These studies, when replicated across a number of products in a class, often used different primary and secondary efficacy endpoints and were consequently not suitable source material for an indirect comparison and as such breached Clauses 7.2, 7.3 and 7.4.

The SPC for a particular product contained information from studies designed specifically for that particular product. This was reinforced by European Commission Guidelines on SPCs which stated under the 'Principles of Presenting Information' that:

> 'The SPC provides information on a particular medicinal product; therefore it should not include reference to other medicinal products (e.g. through statements such as 'Like other medicines of the same class…') except when it is a class warning recommended by a competent authority.'

Merz stated that it was clear from this guidance that each regulatory study stood alone and could not be assumed to be appropriate for comparison with another product in its class purely because it had contributed to the granting of the same or similar indication as another product.

Merz therefore considered that it was unacceptable and misleading to derive dose ratios and make indirect comparisons between products purely on the basis of their listing in an SPC. Breaches of Clauses 7.2 and 7.3 were alleged.

To support its allegation Merz highlighted the differences in design of the registration trials for Dysport and Xeomin for their respective licences in upper limb spasticity (ULS). These registration studies were used to inform Section 4.2, Posology and method of administration, of the respective SPCs. Merz summarised the different endpoints and treatment protocols used in these studies:

Xeomin's ULS registration study, Kanovsky *et al* (2009)
- Primary endpoint:
  - response (defined as a ≥1 point improvement in Ashworth Score) for wrist flexors at week 4
- Treatment protocol:
  - required the mandatory treatment of muscles involved with wrist flexion (to ensure the primary endpoint could be credibly analysed), however up to 13 muscles in total could be treated, dependent on the clinical pattern of spasticity.
  - this led to the increased response in secondary endpoints, and also a higher maximum dose, because more muscles were treated
  - outcomes: primary and secondary endpoints were met

Dysport's ULS Registration study, Bakheit *et al* (2001)
- Primary endpoint:
  - the best change from baseline in Modified Ashworth Score (out of the elbow, wrist or finger joints) at week 4
  - the Modified Ashworth Score was a different scale to the Ashworth Score used in Kanovsky
- Treatment protocol:
  - required the mandatory treatment of 5 specific muscles. No other muscles could be treated, therefore limiting the maximum dose
  - outcomes: primary endpoint met, but many secondary endpoints were missed.

Merz noted that the use of indirect comparisons from different studies was tested in Case AUTH/2199/1/09, where the Panel ruled breaches of Clauses 7.2 and 7.3. The Panel ruled on the use of three different studies presented in such a way so as to invite the reader to compare different trial endpoints by placing the trials in a single box. To the right-hand side of the boxed graphs was a short description of the primary endpoints of each study. The endpoints were not the same for each trial. The references for the four different studies were not given with the endpoints, nor anywhere else on the page. Below the description of the endpoints was the statement 'NB: Caution should be exercised when using indirect comparisons across trials'. In the Panel's view this statement did not negate the incorrect implication that an indirect comparison of the data was valid.

In the present case (Case AUTH/2778/7/15) Merz stated that not only did Ipsen tabulate the initial and maximum doses recommended in the individual product SPCs, which invited readers to directly compare the registration dosages and assume equivalent or materially similar outcomes would be achieved, it went further because it wrongly extrapolated these data in the form of a dosage ratio. Merz alleged that the presentation of the data in this manner was misleading in breach of Clauses 7.2 and 7.3. There was no statement to caution the reader

that the endpoints of the registration studies might be different or that indirect comparison might not be advisable or warranted.

Merz stated that in its view, Ipsen's commercial aim was to cause confusion, or imply some form of non-linear/unpredictable dose response between BoNT-A products. By constructing a table of dose ratios by extrapolating data which were fundamentally not suitable for comparison, the implicit claims of the item could not be substantiated and were misleading. Merz alleged breaches of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Ipsen submitted that the leavepiece was designed to demonstrate that even when the dosages as presented in the three SPCs (Dysport, Botox and Xeomin) were compared the derived ratios varied across indications and even differed between initial and maximum doses within the same indication. The leavepiece thus supported the message that a single dose ratio could not be applied in a blanket fashion.

Ipsen submitted that the content and intention of the leavepiece was set out clearly and accurately in the heading ie that doses as stated in the SPCs were compared and not the registration studies as alleged. The registration studies, regardless of age or phase, were the basis for the marketing authorization and the terms of the SPC; the fact that the studies were of different designs or to different standards did not impact at all on the legal conditions embodied in the product licence. Ipsen stated that it was clear from the outset that it had not compared or intended to compare the registration studies for the three medicines, however SPC doses as approved by the regulatory authority for the three products were compared where possible. The wording on the three SPCs were not entirely consistent and Ipsen strove to compare like-for-like where possible to demonstrate the challenge. Where the SPC wordings were significantly different, Ipsen ensured that this was clear in the table, in accordance with the supplementary information to Clause 7.2.

The subheading of the leavepiece clearly stated that the ratios were derived from the SPC, and that the piece was intended to highlight the variation in dose ratios across indications. The piece did not and was not intended to recommend a single fixed ratio. It was stated in bold above the table that botulinum toxin units were not interchangeable and prescribers were advised to consult the products' SPCs for full prescribing information.

The heading made it clear from the outset that the intention of the leavepiece was to highlight the variation in dose ratios across indications; it did not 'invite the reader to make a direct comparison of the registration dosages and assume equivalent or materially similar outcomes would be achieved' as alleged by Merz. Ipsen submitted that the leavepiece contained factual, regulatory approved, information on recommended initial and maximum doses from the SPCs for Dysport, Botox and Xeomin.

Ipsen noted Merz's concerns with regard to comparing regulatory studies, but noted that the leavepiece did not directly, or indirectly, compare or refer to the regulatory studies for the three products and therefore Ipsen submitted that the leavepiece was not in breach of Clauses 7.2, 7.3 and 7.4 on the basis of an inappropriate comparison of regulatory studies as alleged by Merz.

In Ipsen's view the European Commission Guidelines on Summaries of Product Characteristics presented by Merz covered the principles of presenting information within a single SPC and had no bearing on comparing information stated in one SPC with another.

With regard to Case AUTH/2199/1/09, Ipsen stated that the company found in breach had actually compared three different studies inappropriately (as graphs) and was ruled in breach. That case had no bearing on the matter in hand as Ipsen's leavepiece did not contain any direct or indirect comparison of the data contained within the regulatory studies.

Ipsen agreed that comparisons should only be made on a like-for-like basis; therefore, given that the SPCs, at least in terms of dosing guidelines in Section 4.2, reflected the highest level of clinical trial evidence available to the regulatory authority and that the indications for the three products were identical in some instances (which indicated that the MHRA believed that the condition listed eg blepharospasm, represented a single, defined clinical entity rather than a spectrum) it was not unreasonable to deduce a putative dose ratio or range of ratios based purely on the SPCs as it further underlined the non-interchangeability of the toxins.

Ipsen noted Merz's allegation that by tabulating the initial and maximum doses recommended in the individual SPCs, Ipsen had 'invited readers to directly compare the registration dosages and assume equivalent or materially similar outcomes would be achieved'. However, Ipsen submitted that it had presented factually accurate information from the three SPCs in order to demonstrate to prescribers that the SPC dosages should not be directly compared by highlighting the variation in dose ratios across the indications.

Ipsen submitted that the leavepiece accurately reflected the current SPCs for all toxins. It did not mislead and was, for the most part, a matter of fact. The only derived ratio was one deduced directly from the SPCs themselves, so there was no breach of Clause 7.2.

Ipsen noted that Clause 7.3 related to comparisons and submitted that as the majority of the leavepiece was taken directly from the SPCs and the medicines were intended for the same purpose with relevant features ie the initial and maximum recommended doses being compared, there was no breach of this clause.

The information in the leavepiece was taken directly or derived directly from the SPCs, which were referenced, and therefore Ipsen denied a breach of Clause 7.4.

PANEL RULING

The Panel noted that Dysport and Xeomin were both presented in vials containing varying units of botulinum toxin. The Dysport SPC stated that the units of Dysport were specific to that preparation and were not interchangeable with other preparations of botulinum toxin. Similarly, the Xeomin SPC stated that due to unit differences in the LD50 assay, Xeomin units were specific to Xeomin. The Panel considered that this presented a problem to prescribers should they ever need or want to switch a patient from one BoNT-A product to another. The Panel noted that inter-company dialogue showed that Ipsen believed that during the tendering process, Merz had on more than one occasion proposed that a blanket 4:1 switch from Dysport units to Xeomin units, regardless of indication, would be clinically appropriate and offer economic benefit. In that regard the Panel noted that Xeomin was not licensed for all of the same indications as Dysport.

The Panel considered that the leavepiece at issue clearly compared the dosage information taken from the SPCs for Dysport, Botox and Xeomin. SPC dosage particulars were of course derived from registration studies but the Panel did not consider that the leavepiece was a comparison of these studies *per se* as alleged. In that regard the Panel ruled no breach of Clauses 7.2, 7.3 and 7.4 of the Code. The Panel noted that the leavepiece was produced in order to counter a claim that a dose ratio of 4:1 could be applied across the board when changing patients from Dysport to either Botox or Xeomin. In terms of recommended initial doses of shared indications for Dysport and Xeomin, only one dose ratio was stated in the leavepiece ie 1.6:1 for the treatment of blepharospasm. In terms of maximum doses for the two medicines (see Point 2 below) dose ratios of 3.3:1 and 2.4:1 were given for cervical dystonia and for blepharospasm respectively. This countered a blanket switch at 4:1. Nonetheless, in the Panel's view, the final column appeared to give unequivocal, recommended Dysport:other BoNT-A dose ratios for each of the five indications listed. In the Panel's view this was misleading as each ratio given was based on an indirect comparison of SPC dosage particulars for Dysport and the other medicine, not on a head-to-head clinical study of the two. Breaches of Clauses 7.2 and 7.3 were ruled. The claims could not be substantiated; a breach of Clause 7.4 was ruled.

2 Inappropriate use of maximum licensed doses

COMPLAINT

Merz stated that a dose ratio was a comparison between the doses of two medicines. The clinical purpose of providing a dose ratio was generally to identify a dose-response relationship between different medicines and provide guidance when changing from one to another.

The maximum licensed dose of a medicine was usually a measure of the safety/toxicity profile of that particular medicine. When presenting comparative ratios or maximum dosages it was important to consider that as a consequence of switching from one medicine to another, an unsafe dosage of the new medicine might be administered. Merz alleged that to ignore the potential consequences of switching products at the maximum dosage did not encourage the rational use of medicine in breach of Clause 7.10. An illustration of this risk was presented below from the 'Cervical dystonia' section of the table:

In the table, a maximum dose of 1,000 units of Dysport, a maximum dose of 300 units of Xeomin, and the resultant dose ratio of 3.3:1 (Dysport:Xeomin), was presented. These data were derived from the Section 4.2 of the SPCs which were reproduced below:

Dysport: 'Doses within the range of 250-1000 units are recommended, although the higher doses may be accompanied by an increase in side effects, particularly dysphagia. The maximum dose administered must not exceed 1000 units.'

Xeomin: 'Normally, in practice, the total dose administered does not exceed 200 units. Doses of up to 300 units may be given.'

Merz concluded that in normal circumstances the maximum dosage for Dysport and Xeomin would be 1000 units and 200 units respectively. Given the established safety risks associated with overdose on BoNT-A preparations, and the clear guidance in Section 4.4 Special warnings and precautions for use of the Xeomin SPC outlined below, the difference between 'normal' and 'unusual' practice could be considered very important.

> 'Undesirable effects related to spread of Botulinum toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.'

By presenting a dosage conversion of 3.3:1 (Dysport:Xeomin) the leavepiece invited physicians to consider a patient receiving a dosage of 750-1000 units of Dysport (recommended range of 250-1000 units), to require 227-300 units of Xeomin should they be switched. These figures were well above the normal recommended dosage of 200 units of Xeomin. No clear warning or guidance about the actual SPC wording or implications was given. Merz alleged that the derivation of dose ratios through extrapolation of data which was not suitable for comparison, presented an incomplete analysis, was fundamentally misleading, did not encourage rational use and was not in the interest of patient safety. Merz thus alleged a breach of Clause 7.10.

RESPONSE

Ipsen submitted that the leavepiece accurately reflected the current SPCs for all toxins and accurately described the derivation of the ratios.

Ipsen agreed with Merz that the studies that informed the SPC were designed for each particular product and conducted in different eras and under

different conditions but led to a common regulatory inclusion in the product licenses. The two commonly used measures of efficacy and toxicity were the 'minimum effective dose', which gave an indication of the dose below which no meaningful clinical effect was seen, and the 'maximum tolerated dose' above which tolerability or safety issues outweighed any clinical benefit. Therefore the therapeutic window for any given product was defined by these two parameters. For the toxins in question, these had been translated into Section 4.2 of the SPCs as the recommended initial and maximum doses.

The leavepiece was not designed or intended to recommend a dose ratio and did not encourage inappropriate use of any of the medicines. The purpose was to encourage rational use of the toxins and discourage the use of a single dose ratio across indications and populations. Ipsen submitted that patients could be harmed if a single dose ratio was applied across an entire health economy. Therefore, Ipsen denied a breach of Clause 7.10.

PANEL RULING

The Panel noted its comments above at Point 1 and its view that the final column of the leavepiece appeared to give unequivocal, recommended Dysport: other BoNT-A dose ratios for each indication listed. With regard to the treatment of cervical dystonia the Panel noted that the Xeomin SPC stated that the total dose administered did not usually exceed 200 units but that doses of up to 300 units might be given. The leavepiece at issue however stated, without explanation, that the recommended maximum dose of Xeomin was 300 units. The maximum recommended dose for Dysport in the treatment of cervical dystonia was simply stated to be 1000 units although the SPC stated that whilst doses within the range of 250-1000 units were recommended, the higher doses might be accompanied by an increase in side effects, particularly dysphagia. The resultant dose ratio for Dysport:Xeomin at the maximum dose of each was stated to be 3.3:1. Overall the Panel considered that the references to the maximum doses of Dysport and Xeomin in the leavepiece did not accurately reflect the information given in the SPC or even alert the reader that more details in particular about side effects should be sought. In that regard the Panel did not consider that the statement at the top of the table that the products' SPCs should be consulted for full prescribing information was sufficient. In the Panel's view, the simplistic way in which the information had been presented did not encourage the rational use of the medicines. A breach of Clause 7.10 was ruled.

B 'Botulinum Toxins – The Ratio Challenge' leavepiece

Table 1 of the leavepiece detailed the results of a systematic review of clinical studies which were conducted to determine or test an hypothesised dose ratio between Dysport, Xeomin and Botox. Table 2 presented data from studies published after the systematic review was conducted (February 2012).

1 The leavepiece did not reflect the balance of evidence, and was out of date

COMPLAINT

Merz was concerned that claims in the leavepiece were misleading and did not reflect the balance of evidence in breach of Clause 7.2. By providing an incomplete analysis of the data, Ipsen had deliberately failed to represent publications which conflicted with its message.

Merz stated that readers would base their judgement on the summary of the methodology and description of the inclusion criteria for the meta-analysis shown on the front page of the leavepiece:

> 'A systematic review … aimed to retrieve all relevant published studies that report data conducive to the determination of a dose equivalence ratio of Dysport in comparison to Botox and Xeomin …'
>
> '77 studies were identified … reviewed to find studies which specifically aimed to either determine a dose ratio or test a hypothesised dose ratio between Dysport and Botox or Xeomin. There was no restriction by study design and therefore both prospective and retrospective studies were included.'
>
> '11 studies relevant to this analysis approach were identified and are reviewed in Table 1. A further study, published after the review, is included in Table 2.'

Merz stated that at least two studies (Cossar and Cozens 2015 (abstract/poster) and Grosset *et al* 2015 (publication)) which involved Dysport and Xeomin would meet the above criteria and could have been included in Table 2 as 'further studies'. Breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

Ipsen explained that it instigated a systematic review which was conducted in February 2012 by a life sciences consultancy. The findings of this review were presented in the leavepiece now at issue, 'Botulinum Toxins – The Ratio Challenge'. With biologicals, such as botulinum toxins, dose ratios were very complicated and subject to inherent variation. The leavepiece was designed to demonstrate this inherent variation and to remind the customer of all the factors that could influence a perceived ratio. The section of the leavepiece headed 'The Dose Equivalence Ratio Questions:' was intended to challenge a customer's perception on the existence of a fixed dose ratio and to determine if there was any change following a discussion of the data. Ipsen was frequently asked to provide a specific equivalence or switch ratio as it would simplify cost comparisons and the tender process so it needed materials to allow the field force to explain the complexity of issues surrounding a potential switch and highlight the lack of interchangeability between the products.

Ipsen noted Merz's concern that two recently published studies (Cossar and Cozens and Grosset *et al*) were not included in the systematic review. This was because when the systematic review was conducted in February 2012, neither study had been

published. The more complex question was whether or not these two studies (and any other relevant studies published after February 2012) altered the balance of evidence from the systematic review.

The systematic review identified 77 studies which were screened and required to meet pre-defined eligibility criteria. Eleven studies met these criteria and were the subject of the leavepiece, with one further study published after the systematic review was completed in 2012, but meeting all the eligibility criteria, included as a separate item.

Ipsen submitted that the leavepiece summarised key details from the 12 studies and posed a series of questions on dose ratio – which were not answered *per se*. In fact, the leavepiece made no real claims at all although it did report on the 'clinically equivalent dosing ratio' stated in each study. It was clear from these that there was not a fixed, or set, dosing ratio between toxins (therefore again in line with Case AUTH/2380/1/11). Even if Cossar and Cozens and Grosset *et al*, assuming they met the eligibility criteria for the systematic review, were included, this would only add another potential ratio; it would not 'set' the ratios to a single figure. Ipsen noted that Cossar and Cozens was published in March 2015, a month before the initial inter-company complaint was received in April 2015 despite the fact that the leavepieces at issue had been used since March 2013, and were re-approved following an update to the prescribing information in January 2014.

Ipsen stated that the systematic review was repeated in September 2014 with 106 studies now identified, of which 16 met the eligibility criteria. The conclusions had not changed, with no consistent dosing ratio identified between Dysport and other BoNT-A products either across different indications or for any of the single indications assessed.

Ipsen noted Merz's suggestion that the two studies published in 2015, for which Merz provided editorial funding, could now be added to Table 2 in the leavepiece. Ipsen was concerned that Merz did not proffer inclusion of the two 2015 studies in the leavepiece during inter-company dialogue when asked what amendments to the leavepiece would satisfy Merz. However Ipsen stated it would need to ensure that the studies – and any other relevant studies – met the pre-defined criteria set in the meta-analysis design.

Ipsen maintained that the message of the leavepiece would not change with the addition of the two publications, as the 4:1 ratios concluded in these publications simply added to the plethora of ratios already published and would strengthen the argument that a single, fixed ratio could not be recommended or achieved across different indications.

Ipsen submitted that the leavepiece was an accurate and up-to-date reflection of the evidence available and it therefore denied breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the leavepiece at issue presented the results of a systematic review in February 2012 of the published data that was able to show a dose equivalence ratio for Dysport in comparison to Botox and Xeomin. Seventy-seven studies were identified of which 11 met the eligibility criteria. At the time, no relevant studies were identified which compared Dysport and Xeomin and so the data presented in the leavepiece only related to Dysport and Botox. The Panel noted Ipsen's submission that a subsequent systematic review conducted in September 2014 identified 106 studies, of which 16 met the eligibility criteria. In early 2015 two studies (both with editorial support from Merz) had been published which had looked at switching from Dysport to Xeomin at about a 4:1 dose ratio (Grosset *et al* and Cossar and Cozens); it appeared that Grossett *et al* had been published electronically ahead of print in October 2014. Merz submitted that these studies would meet the eligibility criteria set for the systematic review conducted in 2012 although Ipsen was not certain on that point. The Panel noted that both Grossett *et al* and Cossar and Cozens concluded that when switching patients from Dysport to Xeomin the dose ratio was approximately 4:1. The Panel noted that the leavepiece was part of a campaign to dispel claims that there was a blanket 4:1 dose ratio for Dysport:other BoNT-A products. Inter-company dialogue showed that Ipsen believed that during the tendering process, Merz had on more than one occasion proposed that a blanket 4:1 switch from Dysport units to Xeomin units, regardless of indication, would be clinically appropriate and offer economic benefit. The Panel noted Ipsen's submission, however, that it was anecdotally aware that where clinics or health economies applied such a switch strategy, their patients required further titration which resulted in a 4:1 ratio not being met, and therefore cost savings could not be realised. The Panel further noted that Xeomin was not indicated for all of the same indications as Dysport.

The Panel noted that the leavepiece (dated January 2014) detailed a meta-analysis conducted in February 2012; it had not been updated to reflect the meta-analysis conducted in September 2014 and nor did it include data on Dysport:Xeomin which had since been published. The front page of the leavepiece clearly stated that 'no studies compared Dysport and Xeomin'. In so much as it did not detail the 2014 meta-analysis (even assuming that neither Grossett *et al* nor Cossar and Cozens met the eligibility criteria) the Panel considered that the leavepiece was not based on an up-to-date evaluation of all the data. A breach of Clause 7.2 was ruled. In the Panel's view, readers would assume that all of the relevant data had been included which was not so. In that regard the comparisons made were misleading and a breach of Clause 7.3 was ruled.

2 The use of both leavepieces together

COMPLAINT

Merz stated that the use of leading questions, 'Does a single dose ratio exist?', 'Does a dose ratio exist at an individual patient level?' etc was controversial, as it did not know how Ipsen representatives were briefed to use this item.

If the two leavepieces were used in association with one another, the leading questions asked by 'The

Ratio Challenge' leavepiece could be answered by the 'Comparison of SPC Doses' leavepiece, which provided a seemingly random set of dosage ratios for each indication. In this instance the absence of evidence that a single fixed dosing ratio existed could not be equated to proof that a fixed dosage ratio did not exist.

Therefore Merz alleged that this leavepiece, and particularly the way it would be used, breached all the above clauses stated for the previous 'Comparison of SPC Doses' leavepiece. Breaches of Clauses 7.2, 7.3 and 7.10 in this regard were alleged.

RESPONSE

Ipsen noted that Merz's view that the question 'Does a dose ratio exist at an individual patient level?' was controversial did not make it in breach of the Code. Indeed, the questions within the leavepiece were designed to be thought-provoking and to emphasise the controversy that existed.

Ipsen was confident that the sales team briefing on both leavepieces was sufficiently robust to ensure appropriate and responsible use. Indeed, the two leavepieces were designed to be used together. The question to the reader was, based on the variation in dose ratios demonstrated by comparing the SPCs and based on a robust systematic review; did the reader believe that a single dose ratio could be replicated within a health economy, across a range of indications, treated by multiple injectors?

As the briefing document was commercially confidential, Ipsen provided the following summary. The sales team was briefed to ask 'The Dose Equivalence Ratio Questions', before discussing the data contained within the leavepieces, but not to answer or discuss these questions in depth.

Representatives would then discuss the data from the systematic review and Table 2, and from the SPCs, and highlight the variation in dose ratios across and within indications. They then closed the conversation by referring back to the questions to check whether or how the data had changed the customer's perception with regard to dose ratios.

In relation to Merz's comment 'In this instance the absence of evidence that a single fixed dosing ratio exists could not be equated to "proof" that a fixed dosage ratio does not exist.', Ipsen submitted that the leavepieces did claim that a fixed ratio did not exist on a population basis. A fixed ratio might exist for a single patient with a specific condition, treated by a single injector, but – as amply demonstrated – it had thus far eluded substantiation. As stated before, the question that these leavepieces aimed to address was whether (based on the published literature and SPCs) a single fixed ratio could be applied or replicated across an entire health economy and whether it was appropriate to base claims on cost savings on this assumption.

Ipsen submitted that the sales team had been adequately briefed and that using the two leavepieces together was not in breach of Clauses 7.2, 7.3 and 7.10.

PANEL RULING

The Panel noted that the representatives' briefing material (April 2013) for the leavepiece detailed two key points. The first point was that there were no publications comparing Dysport and Xeomin and as part of that point there was no evidence base supporting a ratio and SPCs were the only comparison and guidance. The Panel noted that the claim that there were no publications comparing Dysport and Xeomin was now out-of-date; Grossett *et al* had been published electronically in October 2014 and in hard copy in early 2015 and Cossar and Cozens was published in March 2015. The reference to the SPCs providing the only comparison and guidance would, in the Panel's view, on the balance of probabilities lead to a discussion of the 'Comparison of SPC Doses' leavepiece, at issue in Point 1 above. In that regard the Panel considered that the two leavepieces were inextricably linked and that its rulings at Point 1 above of a breach of Clauses 7.2, 7.3 and 7.10 applied to their combined use.

* * * * *

During its consideration of this case, the Panel was concerned to note that inter-company dialogue showed that Ipsen believed that during the tendering process, Merz had on more than one occasion proposed that a blanket 4:1 switch from Dysport units to Xeomin units, regardless of indication, would be clinically appropriate and offer economic benefit. In that regard the Panel noted that Xeomin was not licensed for all of the same indications as Dysport. The Panel further noted Ipsen's submission that anecdotally it knew of reports where a 4:1 switch strategy had been used with the result that patients required further titration and the anticipated cost savings were not realised. The Panel queried whether Cossar and Cozens and Grossett *et al* were robust enough to base a blanket claim of a 4:1 dose ratio Dysport:Xeomin regardless of the indication. The Panel requested that Merz be advised of its concerns in this regard.

Complaint received **7 July 2015**

Case completed **3 September 2015**

GENERAL PRACTITIONER v MERCK SHARP & DOHME

Conduct of a representative

A general practitioner complained about the conduct of a named representative who, at the time, worked for Organon.

The complainant alleged that the representative was particularly close and openly physically intimate with his GP partner who had told reception staff that the representative was always to be granted access to the practice. The complainant objected to the behavior and noted that although it was agreed that representatives would not be seen by an individual partner, they did not comply. The complainant stated that the GP partner's relationship with the representative had been longstanding and included her attending and providing funding for a practice barbecue party.

The complainant stated that the representative told the practice manager that he had made inappropriate comments to another representative who could have complained but did not do so. The GP partner relied on the representative's report to make allegations against the complainant.

The complainant subsequently declared that allegations made by the representative had been used by his GP partner in legal proceedings and in a statement to the General Medical Council (GMC). Merck Sharp & Dohme was so informed.

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

The Panel noted that all complainants had the burden of proving their complaint on the balance of probabilities. Complaints were judged on the evidence provided by the parties. The Panel noted that in this case the complainant had referred to the conduct of a representative which had allegedly occurred when the representative worked for a company which through two acquisitions, became the responsibility, in 2010, of Merck Sharp & Dohme. The complainant had not provided any evidence to support his allegations. The representative in question no longer worked for Merck Sharp & Dohme and relevant historical records from the time that she worked for Organon/Schering Plough were no longer available. In the Panel's view, given the circumstances, this was not unreasonable.

The Panel noted Merck Sharp & Dohme's submission that two line managers both remembered the representative as an exemplary employee. In that regard, the Panel queried why, if the representative had conducted herself as alleged, the practice had not complained about her behaviour at the time. Neither the complainant nor Merck Sharp & Dohme had referred to such a complaint.

The Panel did not know the precise date in 2008 of the alleged activities, but pragmatically decided to make rulings in this case according to the 2008 Code.

The Panel decided that it had no evidence to show that the representative had funded a practice barbeque as alleged nor to show that the representative had not complied with the practice's wishes that representatives would not be seen by individual partners. No breaches of the 2008 Code were ruled. The Panel noted its rulings and considered that it had no evidence to show that the representative had not maintained a high standard of ethical conduct; no breach was ruled including no breach of Clause 2 of the 2008 Code.

A general practitioner complained about the conduct of a named representative when she worked for Organon.

COMPLAINT

The complainant alleged that the representative enjoyed a particularly close and openly physically intimate relationship with his GP partner who had issued standing orders to reception staff that she was always to be granted access to the practice. It was their practice to sit together on a sofa and engage in playful physical behaviour. The complainant stated that he objected to this behaviour and, although it was agreed that representatives would not be seen by an individual partner, they did not comply.

The complainant stated that the representative reported to the practice manager that he had made inappropriate comments to another representative although he understood that his alleged victim was invited to make a complaint but did not do so. The complainant explained that his GP partner relied on the representative's report to make allegations against him.

The complainant stated that the relationship between the GP partner and the representative had been longstanding and included her attending, and funding at his invitation, a practice barbecue party held at the complainant's home in about 2008. The representative also invited practice staff to her party in 2008.

When writing to Merck Sharp & Dohme, the Authority asked it to consider Clauses 2, 9.1, 15.2, 15.4 and 22.1 of the 2015 Code. It was noted that depending upon when the activities at issue occurred, the equivalent clauses in other editions of the Code might be relevant.

The complainant subsequently declared that allegations made by the representative had been

used by his GP partner in legal proceedings and in a statement to the General Medical Council (GMC). Merck Sharp & Dohme was so informed.

RESPONSE

Merck Sharp & Dohme stated that it was extremely disappointed that a GP felt compelled many years after the alleged events to complain to the PMCPA. Given the elapsed time, investigation into the matter had been very difficult. Nevertheless, the company took any allegation of inappropriate conduct of its staff very seriously and immediately launched a full investigation.

Merck Sharp & Dohme submitted that it could not interview the representative in question as she left the company some time ago. The complaint related to a time when the representative was employed by Organon Laboratories Limited which was acquired by Schering-Plough Limited in 2007. Schering-Plough Corporation was subsequently acquired by Merck and Co. Inc (called Merck Sharp & Dohme outside of the US and Canada) in 2009; the local business transfer took place in 2010. This transition of businesses and the passage of time meant that Organon's records for 2008 of representative expenses and meetings were no longer available. Further, Merck Sharp & Dohme no longer had access to any archive of Organon standard operating procedures relevant to that time. Merck Sharp & Dohme confirmed that the representative had taken and passed her ABPI examination.

As a consequence of the time between the alleged incident and the complaint being made, Merck Sharp & Dohme stated that it was unable to identify any evidence that the representative funded or attended any practice barbecue or acted inappropriately at the practice. Merck Sharp & Dohme could not verify whether or not practice staff attended the representative's party. Therefore, Merck Sharp & Dohme could find no evidence of having breached Clauses 22.1, 15.4, 15.2, 9.1 or 2 of the 2008-2011 Code or the 2015 Code.

During the investigation, Merck Sharp & Dohme spoke to the representative's line managers from the periods before and after the alleged incident. Both were extremely surprised by the allegations, recalling the representative as an exemplary employee, who always complied with the Code and never had any disciplinary concerns.

Merck Sharp & Dohme noted that although it related to a time period before 2008 as referred to by the complainant, it was relevant that the manager responsible for the representative remembered the GP practice in question, but he had no memory of ever being told about any relationship between the representative and one of the other GPs in the practice. He recalled that the representative was concerned about the complainant's inappropriate behaviour towards her and so he advised her that if she felt uncomfortable she no longer needed to call on the practice. Merck Sharp & Dohme noted that the complainant was subject to a GMC fitness to practice panel hearing where he was issued with a formal warning; he had confirmed this as a conflict of interest with regard to this complaint.

PANEL RULING

The Panel noted that all complainants had the burden of proving their complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The Panel noted that in this case the complainant had referred to the conduct of a representative which had allegedly occurred in 2008, when she had worked for a company which through two acquisitions, became the responsibility, in 2010, of Merck Sharp & Dohme. The complainant had not provided any evidence to support his allegations. The representative in question no longer worked for Merck Sharp & Dohme and relevant historical records of the meetings that she had held or expenses that she had claimed when working for Organon/Schering Plough, were no longer available. In the Panel's view, given the circumstances, this was not unreasonable.

The Panel noted Merck Sharp & Dohme's submission that two of the representative's line managers remembered her as an exemplary employee. In that regard, the Panel queried why, if the representative had conducted herself as alleged, particularly with the complainant's GP practice partner, the practice had not complained about her behaviour at the time. Neither the complainant nor Merck Sharp & Dohme had referred to such a complaint.

The Panel noted that the complainant had referred in particular to activities which allegedly took place in 2008. The 2008 edition of the Code came into operation on 1 July of that year. The Panel did not know the date in 2008 of the alleged activities, but pragmatically decided to make rulings in this case according to the 2008 Code. The case preparation manager had asked Merck Sharp & Dohme to consider the requirements of Clauses 2, 9.1, 15.2, 15.4 and 22.1 of the 2015 Code. The requirements of Clauses 2, 9.1, 15.2 and 15.4 were similar in the 2008 Code and the 2015 Code. Clause 22.1 of the 2015 Code was Clause 19.1 of the 2008 Code.

The Panel decided that it had no evidence before it to show that the representative had funded a practice barbeque in 2008 as alleged; no breach Clause 19.1 of the 2008 Code was ruled. Similarly, the Panel decided that it had not been provided with any evidence to show that the representative had not complied with the practice's wishes that representatives would not be seen by individual partners; no breach of Clause 15.4 of the 2008 Code was ruled. The Panel noted its rulings and considered that it had no evidence before it to show that the representative had not maintained a high standard of ethical conduct; no breach of Clauses 15.2 and 9.1 of the 2008 Code was ruled. Similarly, the Panel ruled no breach of Clause 2 of the 2008 Code.

Complaint received **27 July 2015**

Case completed **2 September 2015**

ABBVIE v BRISTOL-MYERS SQUIBB

Alleged off-licence promotion disguised as a medical symposium

AbbVie alleged that a medical symposium at the British Society of Rheumatology (BSR) 2015, sponsored by Bristol-Myers Squibb, was promotional and encouraged the use of abatacept (Orencia) which was inconsistent with its marketing authorization.

Orencia, in combination with methotrexate (MTX), was indicated for the treatment of moderate-to-severe active rheumatoid arthritis (RA) in adults who had responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs.

AbbVie alleged that although the symposium was presented as being medically led, it was a promotional event in that: it was sponsored by Bristol-Myers Squibb; no new scientific data was presented; abatacept was proactively and prominently discussed and its benefits were emphasised and there were several presentations during the 90 minute symposium, which did not allow for significant two-way exchange with the approximately 100 strong audience.

AbbVie further alleged that the symposium encouraged the use of abatacept inconsistent with its marketing authorization, for example in undifferentiated inflammatory arthritis. Interactive patient case studies used a poll to measure the change in the audience's intention to prescribe with an unlicensed dose.

AbbVie alleged the content of the symposium went beyond what was acceptable for legitimate scientific exchange.

The detailed response from Bristol-Myers Squibb is given below.

The Panel noted that pharmaceutical companies could sponsor symposia at third party meetings. The symposium in question had clearly been characterised as 'A Bristol-Myers Squibb Medical Symposium'; potential attendees would know that it was a pharmaceutical company sponsored event. The material used to advertise the symposium did not include any direct or indirect reference to Orencia. The Panel further noted that the BSR organising committee considered that the symposium topic 'Rheumatoid Arthritis: Is There a Path to Drug-Free Remission' was suitable for discussion at its conference and had included the event in its conference programme and advertised it as such. Invitations had only been distributed in delegate bags of registered attendees. The symposium had not been advertised on a promotional stand and members of Bristol Myers-Squibb's sales force who had attended the conference had been instructed not to discuss the symposium with delegates or invite/direct them to attend. Bristol-Myers Squibb appeared to have no control over who attended the symposium. The Panel noted Bristol-Myers Squibb's submission that the symposium discussed, *inter alia*, new trials which would potentially advance the understanding of the immunological basis of rheumatoid arthritis. The Panel further noted that Bristol-Myers Squibb had emphasised that only its medical department had been involved in organising, reviewing, approving or funding the arrangements and/or materials for the symposium and that there was no commercial input. In that regard the Panel noted that it was immaterial as to which department organised, reviewed, approved or funded the event; it was the content and arrangements which determined whether it was promotional or could be considered the legitimate exchange of medical and scientific information.

The Panel noted that the symposium, which lasted 90 minutes, consisted of three presentations. The programme allowed half an hour for questions and answers and throughout the presentations delegates could use mobile devices to send comments/questions directly to the faculty and speakers. This was in contrast to AbbVie's submission that there were several presentations which did not allow for significant two way exchange with the audience. Feedback from the symposium indicated a high level of audience satisfaction with regard to the discussion session and the opportunity to ask questions.

The first presentation was entitled 'The "at-risk" individual – definition and prospects for therapy'. The presentation included information about APIPPRA and AARIA, investigator initiated abatacept studies. The APIPPRA study set out to investigate Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept and the AARIA study set out to see if abatacept could prevent inflammatory lesions in at-risk patients. Neither use of abatacept was licensed. One of the slides detailing the APIPPRA study was headed 'Why should we try abatacept?' and in this regard the Panel noted Bristol Myers Squibb's submission that the slide set out the rationale for investigating abatacept in the prevention of rheumatoid arthritis. In the Panel's view it was possible that the audience might translate the heading to mean 'Why should I try abatacept [for disease prevention]?', however it was clearly stated in one slide that the APIPPRA study was now recruiting across the UK and the Netherlands. Two of the speaker's earlier slides referred to the PRAIRI study (also an investigator initiated study) which explored disease prevention with rituximab. The Panel noted, that Bristol-Myers Squibb described preventative rheumatoid arthritis studies as new and ground breaking. The first speaker's summary slide stated that clinical trials to date had not identified an intervention proven

to delay or prevent the onset of clinically apparent synovitis and that exploration of the impact of targeted therapies in the at-risk population was still ongoing. In the Panel's view this slide summarised the direction that current research was taking but neither the summary slide nor the presentation was likely to encourage delegates to use Orencia in at-risk patients to prevent rheumatoid arthritis.

The second presentation was entitled 'Biomarkers – a road map for individualized treatment?'. Only six of the 49 slides variously referred to abatacept; many of the other slides referred to other medicines such as methotrexate, rituximab, and tocilizumab. The concluding statement read 'Individualized medicine approaches are anticipated to transform future management of [rheumatoid arthritis] – but we're not there yet!'

The final presentation, entitled 'Early treatment – is this the pathway to drug-free remission?', presented some case studies including audience polls and discussed, *inter alia*, the withdrawal or de-escalation of abatacept. Other medicines were also discussed.

Overall, the Panel considered that the presentations stimulated new ways of thinking with regard to treating and or preventing rheumatoid arthritis. Two of the three current studies examining prevention used abatacept (APIPPRA and AARIA) however the Panel did not consider that the tone or content of the presentations would encourage the audience to use abatacept outside its marketing authorization for disease prevention. The Panel did not consider that the presentations emphasised the benefits of abatacept as alleged; in its view there was no greater prominence given to abatacept than any other medicine.

Overall, the Panel did not consider that AbbVie had, on the balance of probabilities, proven its complaint that the symposium constituted the disguised promotion of abatacept for an unlicensed indication. No breaches of the Code were ruled. Given its view that the symposium did not constitute the promotion of abatacept, the Panel did not consider that delegates needed to be given the prescribing information or the statement regarding reporting adverse events. No breaches of the Code were ruled.

The Panel noted its rulings above and considered that there was no evidence that high standards had not been maintained. No breach of Code was ruled. Given its rulings of no breach of the Code, the Panel consequently ruled no breach of Clause 2.

AbbVie Ltd complained about the content of a medical symposium at the British Society of Rheumatology (BSR) 2015 sponsored by Bristol-Myers Squibb. AbbVie alleged that the symposium was promotional and encouraged the use of abatacept (Orencia) which was inconsistent with its marketing authorization. The symposium ran from 17:45-19:15 on 29 April.

Orencia, in combination with methotrexate (MTX), was indicated for the treatment of moderate-to-severe active rheumatoid arthritis (RA) in adults who had responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor.

COMPLAINT

AbbVie alleged that although the symposium was presented to health professionals as being medically led, it was a promotional event in that: it was sponsored by Bristol-Myers Squibb; no new scientific data was presented; abatacept was proactively and prominently discussed and its benefits emphasised and there were several presentations during the 90 minute symposium, which did not allow for significant two-way exchange with the audience of approximately 100 attendees.

AbbVie further alleged that the symposium encouraged the use of abatacept inconsistent with its marketing authorization, for example in undifferentiated inflammatory arthritis. Interactive patient case studies used a poll to measure the change in the audience's intention to prescribe with an unlicensed dose.

AbbVie alleged the following breaches of the Code: disguised promotion (Clause 12.1) and absence of prescribing information and adverse event reporting (Clauses 4.1 and 4.10); promotion inconsistent with the marketing authorization (Clause 3.2) and discredit to and reduction of confidence in, the industry (Clauses 2 and 9.1). AbbVie alleged the content of the symposium went beyond what was acceptable for legitimate scientific exchange.

RESPONSE

Bristol-Myers Squibb noted that the complaint related to its sponsored symposium at the BSR conference. AbbVie had made a series of non-specific allegations that differed from those which it raised in inter-company dialogue and those specified in its letter to the PMCPA. As AbbVie had not provided the PMCPA (or Bristol-Myers Squibb) with a detailed explanation of why it considered that the sponsored symposium had breached the specified clauses of the Code, it had been difficult to respond in detail to the allegations. Thus, unless otherwise stated, Bristol-Myers Squibb had responded to the most recent allegations – ie those set out above.

Bristol-Myers Squibb noted that in its initial exchange with AbbVie, it proposed that it should ask the members of the faculty for their opinion on the matters about which AbbVie had concern. Bristol-Myers Squibb had not received any response from AbbVie to this suggestion. However, following the escalation of this complaint to the PMCPA, Bristol-Myers Squibb had shared the details of AbbVie's complaint with the three health professionals who delivered the presentations at the symposium together with the Bristol-Myers Squibb response. All three health professionals verbally agreed with the content of the Bristol-Myers Squibb response.

When asked if they wished to comment on the complaint one health professional voluntarily wrote a letter describing the circumstances surrounding the symposium. Bristol-Myers Squibb stated that

whilst the speaker was not an expert on the Code, his letter provided important evidence because he was a truly independent and eminent rheumatologist who acted as a witness on the context and arrangements of the symposium. The speaker's letter was significant because it provided strong evidence to support Bristol-Myers Squibb's rebuttal of AbbVie's allegations about the facts surrounding the symposium. The speaker agreed with Bristol-Myers Squibb that his presentation topic was of high scientific importance to the attendees, that significant medical and scientific exchange did take place and that AbbVie's complaint was based on inaccurate information. It also provided evidence that the BSR conference was a learned society meeting.

Background

Bristol-Myers Squibb submitted that the sponsorship arrangements of this medically led symposium complied with the Code; all of the arrangements were appropriate for a non-promotional symposium.

Bristol-Myers Squibb submitted that its sponsorship was prominently declared on all of the delegates' materials, where the Code required an appropriately worded declaration of the company's involvement. No branding colours, brand names, clusters or logos were used.

The symposium consisted of the following presentations in addition to dedicated time for audience surveys and questions and answers:

Welcome and Introduction; 'The "at-risk" individual – definition and prospects for therapy'; 'Biomarkers – a road map for individualised treatment?' and 'Early treatment – is this the pathway to drug-free remission?'.

Full details of the agenda and copies of the relevant slides were provided.

The only members of Bristol-Myers Squibb UK who had been involved in organising, reviewing, approving or funding the arrangements and/or materials for this symposium were from the company's medical department.

The symposium was not advertised at any promotional booths and the sales force did not distribute invitations or flyers. Invitations were only distributed in the delegate bags of registered conference attendees. Additionally there was a symposium advertisement in the BSR programme, one plasma screen advertisement and two banners.

Bristol-Myers Squibb submitted that it tried to ensure that only attendees sporting full delegate badges attended the symposium. Sales employees were specifically forbidden to attend as per the company briefing of 24 April 2015 which informed the sales team that the company was sponsoring a non-promotional symposium which the sales force should not discuss with BSR delegates nor invite/direct them to attend it. The details of the symposium were not given to members of the sales force and if they received any questions they were to direct the enquirer to the medical information stand.

When Bristol-Myers Squibb received the attendee list from the BSR after the congress, it realised that one of its overseas sales colleagues had attended without making his presence known to the Bristol-Myers Squibb medical team. If the medical team had known of his sales role (albeit from a territory outside the scope of the Code) he would not have been allowed to attend.

Sponsorship by Bristol-Myers Squibb

Bristol-Myers Squibb submitted that it was entirely appropriate for pharmaceutical companies to sponsor a wide range of meetings. The supplementary information to Clause 22.1 stated:

> 'Pharmaceutical companies may appropriately hold or sponsor a wide range of meetings. These range from small lunchtime audio-visual presentations in a group practice, hospital meetings and meetings at postgraduate education centers, advisory board meetings, visits to research and manufacturing facilities, planning, training and investigator meetings for clinical trials and non-interventional studies, launch meetings for new products, management training courses, patient support group meetings and **satellite symposia through to large international meetings organised by independent bodies with sponsorship from pharmaceutical companies.'** (emphasis added).

Bristol-Myers Squibb stated that in addition, its sponsorship was prominently declared on all materials that the delegates would have seen as required by Clause 22.4. The company submitted that sponsorship *per se* did not turn the event into a promotional activity and so it rejected this aspect of the complaint.

No new scientific data was presented

The title of the symposium was 'Rheumatoid Arthritis: Is There a Path to Drug-Free Remission?'. This topic was of great scientific and clinical interest and currently much discussed by rheumatologists. The topic was discussed with each speaker at great length and they agreed with the proposed scientific exchange. Additionally, the BSR organising committee approved it as a suitable topic for scientific discussion at its conference. The BSR 2015 Annual Meeting was advertised by the society as a world-class conference for all health professionals interested in musculoskeletal conditions.

Bristol-Myers Squibb submitted that the speaker agreed with the company that his presentation topic was of high scientific importance to the attendees, that significant scientific exchange did take place and that AbbVie's complaint was based on inaccurate information.

AbbVie's assertion that the symposium was promotional because no new scientific data was presented had not been raised during inter-company dialogue and was incorrect; new data were presented (see below), therefore, Bristol-Myers Squibb rejected this aspect of the complaint.

Whilst legitimate exchange of medical and scientific information was not solely defined by the presentation of new scientific data, the symposium detailed new and current data which reflected advances in rheumatologic medicine. Bristol-Myers Squibb submitted that its symposium included discussion of new data as well as new clinical trial designs, which would potentially advance the understanding of the immunological basis of rheumatoid arthritis. This included the clinical trial designs for the recently completed PRAIRI (rituximab) study as well as the recently initiated APIPPRA and AARIA (abatacept) studies. There were also discussions on data from the following recently published or presented studies; ACT-RAY (tocilizumab), AVERT (abatacept), DRESS (adalimumab and etanercept), HONOR (adalimumab) and the Cochrane review of de-escalation and withdrawal of anti-TNF treatment strategies.

Abatacept was proactively and prominently discussed and its benefits emphasised

Bristol-Myers Squibb acknowledged that the event included data about many agents used to treat rheumatoid arthritis, including abatacept, all of which were proactively discussed in the interest of an open and balanced scientific exchange. It was unreasonable of AbbVie to expect a company-sponsored symposium at a learned society event, addressing issues relating to the management of rheumatoid arthritis, not to mention particular medicines. Bristol-Myers Squibb noted that AbbVie had not explained why it considered abatacept had been prominently discussed.

All presentations presented data on abatacept, as well as many other rheumatoid arthritis treatments. Medicines used in the treatment of rheumatoid arthritis were frequently mentioned by non-proprietary names and over the three presentations of 126 slides, they appeared on or were discussed as follows; abatacept 23 slides, anti-TNFs (adalimumab, certolizumab pegol, etanercept and infliximab) 42 slides, rituximab 9 slides, corticosteroids and synthetic DMARDS on 20 slides and tocilizumab on 3 slides. In addition, no claims for any products, including abatacept, were made.

Bristol-Myers Squibb did not believe that abatacept was given greater prominence than any of the other rheumatoid arthritis medicines. The use of the word abatacept was fair and balanced when considering the use of the medicine name in line with the content and context of each data presentation and within the overall symposium itself.

Biologic DMARDs with different modes of action were discussed. Abatacept was a T-cell co-stimulatory modulator. Four of the other medicines discussed were of the same mode of action ie anti-tumour necrosis factor (anti-TNFs); adalimumab, certolizumab pegol, etanercept and infliximab. Rituximab was an anti-CD20 and tocilizumab was an anti-Interleukin 6 (anti-IL6) biologic DMARD.

Preventative rheumatoid arthritis studies were new and ground breaking within rheumatology. There was a hypothesis that rituximab and abatacept might help to prevent rheumatoid arthritis as they worked earlier in the rheumatoid arthritis inflammatory cascade by targeting B-cells and T-cells respectively. In rheumatoid arthritis, activation of T-cells led to activation of B-cells, antibody production and the subsequent production of several immune mediators which led to the clinical manifestations of rheumatoid arthritis. The first presentation of the symposium detailed three investigator initiated studies, PRAIRI (rituximab), APIPPRA and AARIA (abatacept) as these were the only studies known to the speaker and Bristol-Myers Squibb, which were currently investigating the prevention of rheumatoid arthritis using current rheumatoid arthritis therapies. Therefore abatacept and rituximab were the only two biologic DMARDs that were discussed in this presentation. Additionally steroids and synthetic DMARDs were also discussed as part of this presentation.

Bristol-Myers Squibb submitted that the discussion of abatacept in the symposium, when placed within its proper context of the legitimate exchange of scientific, medical and clinical information, was accurate, balanced, up-to-date, appropriate and non-promotional. Bristol-Myers Squibb thus rejected AbbVie's allegation that abatacept had been proactively and prominently discussed.

Bristol-Myers Squibb noted that AbbVie did not detail how it considered that the presentations had emphasised the benefits of abatacept. The definition of a benefit was 'an advantage or profit gained from something' or in a more commercial setting a 'desirable attribute of a product'. Bristol-Myers Squibb reiterated its comments above regarding the references to abatacept as well as the many other rheumatoid treatments, across all of the presentations.

The subject of the symposium was 'Is There a Path to Drug-Free Remission?' and its three presentations were entitled: 'The "at-risk" individual – definition and prospects for therapy'; 'Biomarkers – a road map for individualised treatment?' and 'Early treatment – is this the pathway to drug-free remission?'. This encompassed the idea that intensive targeted therapies in early or established rheumatoid arthritis might subsequently lead to extended periods of medicine-free remission in a subset of patients. Including the rationale that if the pre-clinical phase of disease could be accurately defined, targeting therapy to those at highest risk of developing the more severe form of disease would potentially prevent or at least delay the onset of rheumatoid arthritis. It would therefore be unrealistic to expect participants to have a proper informed discussion without being able to discuss how any of the current therapeutic options might be used. This did not constitute emphasis of the benefits of abatacept.

Due to a lack of detail and clarity in AbbVie's complaint about what in the presentations it considered had emphasised the benefits of abatacept, Bristol-Myers Squibb addressed AbbVie's concerns about one sentence in one slide of the speaker's presentation. AbbVie mentioned this in its

original letter to Bristol-Myers Squibb. The speaker included one slide containing the text 'Why should we try abatacept?' to explain why the medicine was investigated in the APIPPRA study. In this instance 'try' equated to 'investigate using'. When read within the context of the sequence of the slides presented, Bristol-Myers Squibb submitted that the meaning was appropriate and non-promotional.

Bristol-Myers Squibb strongly refuted the allegations that the benefits of abatacept were discussed let alone emphasised during the symposium; it therefore rejected this aspect of the complaint.

There were several presentations which … did not allow for significant two way exchange

As stated above, the symposium consisted of three presentations and Bristol-Myers Squibb submitted that it had made substantial efforts to ensure that the event was highly interactive in order to facilitate significant two way exchange with the audience. This was achieved by both a dedicated question and answer session of about half an hour as well as by the use of keypads. Bristol-Myers Squibb noted that devices such as telephones and tablets were not simply used to indicate answers to questions posed by the panel, but could be used to send comments or questions to the faculty and speakers during the presentation so that questions could be answered immediately, as well as at the end of the session – thus the keypads enabled delegates to ask questions throughout the symposium. The outputs from the keypads were provided.

The third lecture was specifically designed to encourage delegate participation before and after the lecture and, contrary to AbbVie's allegation, a lively discussion took place with delegates. In addition, discussion on the symposium continued well after the symposium ended as acknowledged by the speaker. Bristol-Myers Squibb noted that the speaker stated that AbbVie was incorrect to allege that there was no significant exchange with the audience and that the symposium 'fostered discussion and debate both during and after the event' as true medical and scientific exchange should. Bristol Myers-Squibb noted that 90% of respondents of the anonymous returned feedback forms stated that they were 'satisfied', 'very satisfied' or 'completely satisfied' with the opportunity to ask questions during the symposium.

Given that delegates had considerable opportunities to ask questions throughout the symposium and that a lively discussion took place, Bristol-Myers Squibb rejected this aspect of the complaint.

The symposium encouraged the use of abatacept inconsistent with its marketing authorization, for example in undifferentiated inflammatory arthritis

Bristol-Myers Squibb noted that AbbVie had not detailed why it considered that delegates had been encouraged to use abatacept in a manner inconsistent with its marketing authorization. Thus, Bristol-Myers Squibb addressed AbbVie's concerns mentioned in its original letter to Bristol-Myers Squibb.

- Prevention of rheumatoid arthritis in patients with ACPA (anti-citrullinated protein antibody) positive arthralgia (APIPPRA study) and delay of progression in patients with undifferentiated inflammatory arthritis (ADJUST study):

Bristol-Myers Squibb noted that preventative rheumatoid arthritis studies were new and ground breaking within rheumatology. This was not currently a licensed indication anywhere in the world for any disease-modifying drug. The supplementary information to Clause 3 allowed the legitimate exchange of medical and scientific information which was outside of the current label for a medicine.

There was a hypothesis that rituximab and abatacept might help to prevent rheumatoid arthritis as they worked earlier in the rheumatoid arthritis inflammatory cascade by targeting B-cells and T-cells respectively. In rheumatoid arthritis, activation of T-cells led to activation of B-cells, antibody production and the subsequent production of several immune mediators which led to the clinical manifestations of rheumatoid arthritis.

Data suggested that individuals with high levels of ACPA were at high risk of developing rheumatoid arthritis. Rituximab affected the production of antibodies by specifically targeting B-cells. Abatacept inhibited T-cell activation, T-cell antibody dependent responses and T-cell dependent B-cell proliferation and thus indirectly impacted antibody production.

The three investigator initiated studies discussed at the symposium, PRAIRI (rituximab study), APIPPRA and AARIA (abatacept studies) were the only studies known to the speaker and Bristol-Myers Squibb which were currently investigating the prevention of rheumatoid arthritis using current rheumatoid arthritis therapies. It was clearly stated during the presentation that the studies were either recruiting or had recently finished recruiting. The speaker's presentation also focussed on the scientific rationale and design of other relevant studies including PROMPT (methotrexate), SAVE and STIVEA (corticosteroids), as well as ADJUST (abatacept). The aim was to discuss studies that had investigated prevention of progression of undifferentiated inflammatory arthritis to rheumatoid arthritis. Discussion of these studies unavoidably meant that the medicines being investigated were mentioned; to have omitted any of these studies would not have been fair or balanced.

As previously stated, the speaker included one slide containing the question 'Why should we try abatacept?' to explain why the medicine was investigated in the APIPPRA study. In this instance, 'try' equated to 'investigate using'. When read within the context of the sequence of the slides presented, the meaning was appropriate and non-promotional. This was not an encouragement to use abatacept in a manner inconsistent with its marketing authorization.

- Use of abatacept in MTX-naïve rheumatoid arthritis (AGREE study) and dose de-escalation of abatacept (AGREE study).

The subject of the third lecture presented by a second speaker ('Early treatment – is this the pathway to drug-free remission?') discussed the concept of how early rheumatoid arthritis treatment might lead to sustained medicine-free remission and if dose reduction was possible to maintain disease remission.

This lecture discussed studies on rheumatoid arthritis therapies that had investigated the prospects of sustained medicine-free remission including synthetic DMARDS, anti-TNF biologic DMARDS (adalimumab, certolizumab, etanercept and infliximab), anti-IL6 biologic DMARD (tocilizumab) and T-cell co-stimulation modulator (abatacept). The objective of this session was to discuss which subsets of patients in remission might be considered for DMARD dose reduction or treatment withdrawal, for example patients with established rheumatoid arthritis vs patients with early rheumatoid arthritis. Discussion of abatacept within the context of the slides presented and data discussed was appropriate and non-promotional.

In its complaint AbbVie referred to the use of interactive patient case studies. Bristol-Myers Squibb noted that AbbVie did not raise its concerns about the use of the interactive poll during the symposium in inter-company dialogue. Bristol-Myers Squibb noted that, contrary to the inference in AbbVie's complaint, only one of the cases presented in the second speaker's presentation referred to abatacept, whilst the other cases referred to other medicines. These cases were presented so as to allow the audience to discuss how a patient who had achieved remission from rheumatoid arthritis might be managed. Cases were presented for three different types of DMARDs including a synthetic DMARD (methotrexate), an anti-TNF biologic DMARD (etanercept) and a T-cell co-stimulatory modulator (abatacept). The same questions were asked following presentation of each case to determine if current treatment should be continued, modified or stopped. The question of how to manage patients who no longer had active rheumatoid arthritis was a valid subject for rheumatologists and discussion on this particular issue was appropriate within the context of a purely scientific meeting. When read within the context of the sequence of slides presented, the questions were appropriate and non-promotional. Bristol-Myers Squibb submitted that the case studies discussed were entirely hypothetical and designed to illustrate some of the points made in the presentations and to stimulate debate amongst the audience and faculty. Bristol-Myers Squibb strongly refuted the allegation that they were intended to encourage off-label use of abatacept or any other DMARD.

As this was a legitimate scientific and medical exchange, Bristol-Myers Squibb rejected this aspect of the complaint.

Summary of symposium

Bristol-Myers Squibb submitted that the symposium was a standalone legitimate scientific and medical exchange organised by its medical department in conjunction with an eminent and independent external faculty. Bristol-Myers Squibb did not intend to repeat the meeting or use the data or information presented or discussed in any way other than to stimulate and encourage legitimate scientific, medical and clinical debate during the symposium.

For the reasons set out above, Bristol-Myers Squibb was satisfied that all of the symposium arrangements and materials met the requirements for a legitimate exchange of scientific clinical information.

Specific clauses

Bristol-Myers Squibb noted that AbbVie's complaint concluded with a list of alleged breaches which appeared to be linked to its overall allegation that the symposium was promotional. Bristol-Myers Squibb thus rejected every alleged breach as it strongly believed it had shown that the event was an appropriate scientific symposium. Nevertheless, for completeness, a response to each specific clause cited was given below, even though it was incredibly difficult to link some aspects to specific allegations as the construct of the complaint was unclear.

Bristol-Myers Squibb submitted that all of the alleged breaches were based on AbbVie's false allegation that the symposium was promotional. Bristol-Myers Squibb refuted this allegation, and all of the associated breaches of the Code in the strongest possible terms.

12.1 – Disguised promotion

Bristol-Myers Squibb had described why, in its view, the symposium complied with the Code and was non-promotional and therefore was not disguised promotion. Company sponsorship was clearly stated and all medicines were appropriately discussed, including Bristol-Myers Squibb's. As previously stated, the topic discussed was of great scientific and clinical interest and was currently the subject of much discussion amongst rheumatologists. The topic for the symposium was discussed with each of the speakers at great length and they agreed with the proposed scientific exchange. Additionally, the BSR organising committee approved the topic as a suitable for scientific discussion at its congress.

The symposium was a standalone, legitimate scientific and medical exchange. Bristol-Myers Squibb considered that the sponsorship arrangements for the symposium complied with the Code and could not be considered disguised promotion.

4.1 – Lack of prescribing information and
4.10 – Lack of adverse event reporting statement

Bristol-Myers Squibb submitted that as this was a non-promotional meeting, the Code did not require either prescribing information or an adverse event reporting statement to be included.

3.2 – Promotion inconsistent with marketing authorization

Bristol-Myers Squibb noted that the symposium was a non-promotional meeting involving medical and scientific exchange as discussed in some detail above. There was no promotion at this event and therefore promotion inconsistent with the marketing authorization did not occur. Preventative rheumatoid arthritis studies discussed were new and ground breaking within rheumatology. This was not currently a licensed indication anywhere in the world for any disease-modifying medicine. Additionally, as described above, the question of how to manage patients who no longer had active rheumatoid arthritis was a valid question for rheumatologists and discussion on this particular issue was appropriate within the context of a purely scientific meeting. The supplementary information to Clause 3 allowed for the legitimate exchange of medical and scientific information which was outside of the current label for a medicine. Promotion inconsistent with the marketing authorization did not occur.

2 – Discredit to and reduction of confidence in, the industry and
9.1 – Maintaining high standards

Bristol-Myers Squibb stated that it had described above and in its letter to AbbVie why the meeting should be considered as legitimate exchange of medical and scientific information. It had gone to great lengths to ensure the symposium complied with the Code and therefore the company submitted that it had maintained high standards and had not engaged in any activity which should be the subject of censure by the PMCPA.

PMCPA Questions

The PMCPA had requested some specific additional information regarding the criteria used to select the faculty, details of how the topic was agreed with the faculty and the number of delegates attending:

The three eminent rheumatologists who comprised the faculty were selected by Bristol-Myers Squibb medical personnel based on their expertise; details were provided.

The subject matter of the symposium was identified by Bristol-Myers Squibb medical personnel, based on interest in this topic at international congresses in recent years, as well as general conversations with UK rheumatologists. In addition, it was approved by the BSR. The overall concept of the symposium was supported by the faculty as being of genuine interest to UK rheumatologists.

The specific topic of 'The "at-risk" individual – definition and prospects for therapy' approved by the BSR was suggested by one of the speakers as the next frontier in rheumatology research.

The rheumatology community's interest in the subject of medicine-free remission was further supported by the volume of data presented at the European League Against Rheumatism (EULAR) Congress, June 2015 in Rome, on the subject of biologic dose modification when remission was achieved. Pharmaceutical companies had organised symposia on these topics including AbbVie which sponsored a non-promotional symposium at EULAR 2015 on managing patients in remission entitled 'Dose tapering after achieving sustained remission - Can we predict disease progression?'.

The content of each presentation of the symposium at issue was developed at the discretion of each speaker following an initial brief from Bristol-Myers Squibb. Further contributions from Bristol-Myers Squibb were made when requested by the speakers and also to ensure the presentations reflected the latest available scientific evidence. Additionally, Bristol-Myers Squibb reviewed the presentations to ensure compliance with the Code. The faculty briefing documents made it very clear that the meeting was to be non-promotional and the content should represent a balanced view of the latest evidence on all relevant therapies. Any mention of abatacept within the speaker presentations were presented within the context of the topic discussed and were done so at the discretion of the faculty.

Bristol-Myers Squibb submitted that correspondence between it, the faculty and the third party agency showed the company's genuine intention to engage in legitimate scientific exchange. The design of the programme had input from the faculty and the final agenda and programme structure were based on comments from the faculty.

Before presenting, the speakers were briefed to deliver non-promotional, fair, balanced, up-to-date and clinically relevant presentations to enhance the audience's scientific knowledge. They were asked to provide an unbiased view of the topics discussed. To keep true with the spirit of scientific exchange and Code requirements, speakers were asked to ensure all data presented was accurate, balanced, fair, objective, unambiguous, based on an up-to-date evaluation of all the evidence, not misleading, capable of substantiation and not disparaging or disrespectful to competitor companies or products.

A list of the 158 attendees was provided.

This event was a standalone legitimate scientific and medical exchange organised solely by the Bristol-Myers Squibb medical department in conjunction with an eminent and independent external faculty. Bristol-Myers Squibb stated that it would not be repeating the meeting or using the data or information presented or discussed in any way other than to stimulate and encourage legitimate scientific and clinical debate at this particular meeting.

As the symposium was non-promotional and did not otherwise meet the requirements for certification as described in Clause 14.3, materials were not certified but they were examined to ensure compliance with the Code.

Bristol-Myers Squibb submitted that throughout this matter it had complied with the spirit and letter of the Code. The symposium was conducted to the highest

standards, in line with the Code, and the company had been fully transparent in demonstrating this.

PANEL RULING

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. The PMCPA Guidance about Clause 3 further stated that 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.

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

The Panel noted that AbbVie had the burden of proving its complaint on the balance of probabilities. The company's complaint was broad in its scope and almost no detail had been provided as to why it alleged that breaches of the Code had occurred.

The Panel noted that it was well accepted that pharmaceutical companies could sponsor symposia at third party meetings. The symposium in question had clearly been characterised as 'A Bristol-Myers Squibb Medical Symposium'; potential attendees would be well aware that they would be attending a pharmaceutical company sponsored event. The material used to advertise the symposium did not include any direct or indirect reference to Orencia (abatacept); brand colours or logos were not used. The Panel further noted that the BSR organising committee considered that the symposium topic 'Rheumatoid Arthritis: Is There a Path to Drug-Free Remission' was suitable for discussion at its conference and had included the event in its conference programme and advertised it as such. Invitations had only been distributed in delegate bags of registered attendees. The symposium had not been advertised on a promotional stand and members of Bristol Myers-Squibb's sales force who had attended the conference had been instructed not to discuss the symposium with delegates or invite/direct them to attend. Bristol-Myers Squibb appeared to have no control over who attended the symposium. The Panel noted Bristol-Myers Squibb's submission that the symposium discussed, *inter alia*, new trials which would potentially advance the understanding of the immunological basis of rheumatoid arthritis. The Panel further noted that Bristol-Myers Squibb had emphasised that only its medical department had been involved in organising, reviewing, approving or funding the arrangements and/or materials for the symposium and that there was no commercial input. In that regard the Panel noted that given the broad definition of promotion in Clause 1.2, it was immaterial as to which department organised, reviewed, approved or funded the event; it was the content and arrangements which determined whether an event was promotional or could be considered the legitimate exchange of medical and scientific information.

The Panel noted that the symposium, which lasted an hour and a half, consisted of three presentations. The programme allowed half an hour for questions and answers and throughout the presentations delegates could use mobile devices to send comments/questions directly to the faculty and speakers. This was in contrast to AbbVie's submission that there were several presentations which did not allow for significant two way exchange with the audience. Feedback from the symposium indicated a high level of audience satisfaction with regard to the discussion session and the opportunity to ask questions. The audience included rheumatologists, nurse specialists, hospital doctors as well as a number of staff from pharmaceutical companies.

The first presentation was entitled 'The "at-risk" individual – definition and prospects for therapy'. The presentation included information about the APIPPRA and AARIA studies both of which were investigator initiated abatacept studies. The APIPPRA study set out to investigate **A**rthritis **P**revention **I**n the **P**re-clinical **P**hase of **R**A with **A**batacept and the AARIA study set out to see if abatacept could prevent inflammatory lesions in at-risk patients. Neither use of abatacept was licensed. One of the slides detailing the APIPPRA study was headed 'Why should we try abatacept?' and in this regard the Panel noted Bristol Myers Squibb's submission that the slide set out the rationale for investigating abatacept in the prevention of rheumatoid arthritis. In the Panel's view it was possible that the audience might translate the heading to mean 'Why should I try abatacept [for disease prevention]?', however it was clearly stated in one slide that the APIPPRA study was now recruiting across the UK and the Netherlands. Two of the speaker's earlier slides referred to the PRAIRI study (also an investigator initiated study) which explored disease prevention with rituximab. The Panel noted, that Bristol-Myers Squibb described preventative rheumatoid arthritis studies as new and ground breaking. The first speaker's summary slide stated that clinical trials to date had not identified an intervention proven to delay or prevent the onset of clinically apparent synovitis and that exploration of the impact of targeted therapies in the at-risk population was still ongoing. In the Panel's view this slide summarised the direction that current research was taking but neither the summary slide nor the presentation was likely to encourage delegates to use Orencia in at-risk patients to prevent rheumatoid arthritis.

The second presentation was entitled 'Biomarkers – a road map for individualized treatment?'. Only six of the 49 slides variously referred to abatacept; many of the other slides referred to other medicines such as methotrexate, rituximab, and tocilizumab. The concluding statement read 'Individualized medicine approaches are anticipated to transform future management of [rheumatoid arthritis] – but we're not there yet!'

The final presentation, entitled 'Early treatment – is this the pathway to drug-free remission?', presented some case studies including audience polls and discussed, *inter alia*, the withdrawal or de-escalation of abatacept. Other medicines were also discussed.

Overall, the Panel considered that the presentations stimulated new ways of thinking with regard to treating and or preventing rheumatoid arthritis. Two of the three current studies examining prevention used abatacept (APIPPRA and AARIA) however the Panel did not consider that the tone or content of the presentations would encourage the audience to use abatacept outside its marketing authorization for disease prevention. The Panel did not consider that the presentations emphasised the benefits of abatacept as alleged; in its view there was no greater prominence given to abatacept than any other medicine. Although feedback on the symposium included one comment, 'Machiavellian strategy to use more abatacept', the Panel noted that it had no information as to which delegate had made that comment; it was not echoed by other feedback comments recorded. The Panel noted that a number of the audience were from other pharmaceutical companies and so it was possible that such a comment could have been made by one of them.

Overall, the Panel did not consider that AbbVie had, on the balance of probabilities, proven its complaint that the symposium constituted the disguised promotion of abatacept for an unlicensed indication. No breach of Clauses 12.1 and 3.2 were ruled respectively. Given its view that the symposium did not constitute the promotion of abatacept, the Panel did not consider that delegates needed to be given the prescribing information or the statement regarding reporting adverse events. No breaches of Clauses 4.1 and 4.10 were ruled accordingly.

The Panel noted its rulings above and considered that there was no evidence that high standards had not been maintained. No breach of Clause 9.1 was ruled. Given its rulings of no breach of the Code, the Panel consequently ruled no breach of Clause 2.

Complaint received **9 July 2015**

Case completed **6 October 2015**

CASE AUTH/2782/7/15

VOLUNTARY ADMISSION BY GLAXOSMITHKLINE

Patient support items distributed from exhibition stand

GlaxoSmithKline voluntarily admitted that patient support items (demonstration devices and training whistles for the Ellipta inhaler) had been handed out at a meeting for nurses organised by a third party.

In accordance with Paragraph 5.6 of the Constitution and Procedure the Director treated the matter as a complaint.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that the Code stated that patient support items must not be given out from an exhibition stand. In contravention of that requirement, however, Ellipta demonstration devices and training whistles had been given out from an exhibition stand at a third party organised meeting. The Panel noted that as all of the exhibition material had been ordered for delivery to the hotel where the meeting was to be held, it was unfortunate that neither the delivery address nor the nature of the items ordered (including an exhibition tablecloth) in themselves did not trigger further enquiry before the items were dispatched. Nonetheless, the representative who had ordered the items and the account manager who was at the meeting had been trained on the provision of patient support items and both should have known that such items could not be given out from an exhibition stand. However, as such items had been so distributed, the Panel ruled a breach of the Code. High standards had not been maintained. A further breach of the Code was ruled.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such. In that regard the Panel did not consider that the matter warranted such a ruling and so no breach of Clause 2 was ruled.

GlaxoSmithKline UK Limited voluntarily admitted a breach of the Code in that that it had handed out patient support items (21 demonstration devices and 17 training whistles for the Ellipta inhaler) from an exhibition stand at a third party meeting for nurses held in April 2015.

In accordance with Paragraph 5.6 of the Constitution and Procedure the Director treated the matter as a complaint.

VOLUNTARY ADMISSION

GlaxoSmithKline stated that in June 2015, a routine internal audit identified a discrepancy between the number of demonstration devices and training whistles issued to a representative and the number of items accounted for. The operations team consequently asked the representative to complete a report outlining what had happened. When this report, including proposed corrective and preventative actions (CAPAs), was reviewed in July, a breach of the Code was identified and the company decided to make a voluntary admission to PMCPA.

Before notifying the PMCPA, further information was requested to understand the exact sequence of events. The representative's manager was asked to contact the individuals involved for further information. The following details were obtained:

On 17 March 2015, the meeting organisers asked a GlaxoSmithKline account manager if GlaxoSmithKline wished to purchase stand space. The account manager agreed that GlaxoSmithKline would exhibit at the meeting.

On 10 April, following a request from the account manager, the representative ordered 25 Ellipta demonstration devices and 25 Ellipta training whistles to be delivered directly to the meeting venue.

The account manager manned the stand at the meeting and handed out 21 demonstration devices and 17 training whistles in breach of Clause 18.2. Each item provided was signed for by the recipient; each recipient had subsequently been verified to be a health professional.

In November 2013, both the account manager and the representative were trained on the process for managing and ordering demonstration devices and training whistles. A copy of the training attendance log was provided.

GlaxoSmithKline stated that the following preventative actions were in progress:

All commercial field team staff had been reminded in writing that it was not permissible to hand out patient support items from exhibition stands.

The current training slide deck on the provision of demonstration devices, whistles and samples had been updated to make it explicit that these items could not be handed out from exhibition stands.

The documentation outlining the process for the management of samples, placebos, demonstrators, testers and other training devices was under review to provide better clarity.

A case study would be developed for sharing with the boarder organisations to ensure that lessons were learnt from this error.

GlaxoSmithKline submitted that this was a case of human error; the individuals involved and their manager had been informed and reminded of

the requirements of the Code with regard to the provision of patient support items.

GlaxoSmithKline stated that it took its obligations for compliance with the Code seriously and was committed to ensuring that all staff were appropriately trained and acted in compliance with the Code.

When writing to GlaxoSmithKline to confirm that the matter would be taken up under the Code, the Authority asked it to provide any further comments it might have in relation to Clauses 2, and 9.1 in addition to Clause 18.2 cited by GlaxoSmithKline.

RESPONSE

GlaxoSmithKline stated that it expected its employees to comply with the Code, laws and regulations, the GlaxoSmithKline Code and policies and maintain high standards at all times. It appeared that an individual had, as a result of human error, acted such as to breach Clause 18.2. GlaxoSmithKline very much regretted this matter. The problem was identified through governance procedures and the deviation brought to the attention of senior managers who took swift and appropriate action. This resulted in the voluntary admission.

Appropriate corrective action was taken in that it had been confirmed that all the individuals to whom the devices had been provided were health professionals, and databases had been updated to record provision of these devices to these individuals. The individual involved was immediately reminded of Clause 18.2.

Preventative action had been taken in the form of a communication to all the commercial field roles reiterating the provisions of Clause 18.2. The training slides about how demonstration devices and training whistles could be provided to customers had been updated with explicit instructions that patient support items could not be handed out from exhibition stands. The documentation outlining the process for the management of samples, placebos, demonstrators, testers and other training devices was under review to provide better clarity and a case study would be developed to share with the broader organisation to ensure that lessons were learnt.

GlaxoSmithKline submitted that it always strove to maintain high standards as required by Clause 9.1 and in this instance it believed that the root cause of the problem was not a lack of process but human error by the representative. GlaxoSmithKline thus submitted that a breach of Clause 9.1 was not warranted as it had taken relevant action to correct the issue as soon as it became apparent.

GlaxoSmithKline was committed to open and transparent behaviour and in that regard it strongly believed that it had acted quickly and transparently to bring this to the attention of the PMCPA. As such, GlaxoSmithKline submitted that it had not brought the industry into disrepute.

In response to a request for further information, GlaxoSmithKline stated that a number of items were ordered for the meeting from a third party provider and despatched en bloc to the venue; a list of the items and quantities ordered was provided. In addition a giant Ellipta model was delivered to the event via a separate company. The model was shipped in a black case so that it was not visible to the public. No exhibition panels were ordered for the meeting. The account manager who attended the meeting had a pull up exhibition stand.

GlaxoSmithKline explained that it classified meetings into two categories - those organised by the company (stand alone meetings) and those organised by other third parties (sponsored meetings). Exhibitions fell into the category of a sponsored meeting; the company's databases did not specifically record a category of exhibition.

GlaxoSmithKline stated that the items required for the meeting were ordered through its electronic ordering system. On receipt of the request, the third party provider responsible for despatching such items including promotional leavepieces, samples or patient support items, would have picked and despatched the items. The third party provider was not required to review all orders manually to determine to where they were to be delivered. Only the representative would have been clear that the ordered items were for an exhibition.

GlaxoSmithKline explained that the number of demonstration devices or other patient support items a representative might order was determined by the relevant brand team and varied from item to item. Up to 25 Ellipta demonstration devices and/or 40 training whistles could be hand delivered to a customer at any one time and representatives could hold up to 50 of each to fulfil customer requests.

GlaxoSmithKline stated that the representative ordered 25 Ellipta demonstration devices and 25 Ellipta training whistles. As these quantities were well within the maximum allowed for a representative to order, an order of this size would not have triggered further enquiry.

GlaxoSmithKline stated that third party sponsored meetings might occur at a variety of venues; its internal ordering system did not have automated validation checks built in for delivery addresses. As such, there was no automated control that would have triggered further enquiry just because a hotel address had been entered. Whilst a manual check of all delivery addresses could be implemented, this would be a large resource implication for a very low number of potential triggers. GlaxoSmithKline considered that a representative's knowledge of the Code should be sufficient to understand the requirements of the Code in relation to what could be provided from an exhibition stand. Unfortunately, on this occasion, the expected standards were not met.

PANEL RULING

The Panel noted that Clause 18.2 stated that items intended to be passed to patients as part of a formal

patient support programme must not be given out from an exhibition stand. In contravention of that requirement, however, 21 Ellipta demonstration devices and 17 training whistles had been given out from an exhibition stand at a third party organised meeting for nurses. The Panel noted that the material needed for the exhibition had been ordered en bloc for delivery to the hotel where the meeting was to be held. In that regard the Panel considered that it was unfortunate that neither the delivery address nor the nature of the items ordered (including an exhibition tablecloth) in themselves did not trigger further enquiry before the items were dispatched. Nonetheless, the representative who had ordered the items and the account manager who was at the meeting to man the stand, had been trained on the provision of patient support items and both should have known that such items could not be given out from exhibition stands. The Panel did not consider that the matter was a failing of one individual as submitted by GlaxoSmithKline. The Panel noted that the prohibition on the provision of patient support items from exhibition stands had been a requirement of the Code since 2011 and so in that regard there should have been a very well established company procedure such that no thought would ever be given to distributing such items from stands. However, patient support items had been distributed from an exhibition stand and so the Panel ruled a breach of Clause 18.2. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such. In that regard the Panel did not consider that the matter warranted such a ruling and so no breach of Clause 2 was ruled.

Complaint received **21 July 2015**

Case completed **19 August 2015**

ANONYMOUS, NON-CONTACTABLE EX-EMPLOYEE v CHIESI

Alleged failure to certify materials

An anonymous, non contactable ex-employee complained that an unapproved presentation on the Code and compliance had been delivered at a Chiesi sales conference.

The detailed response from Chiesi is given below.

The Panel noted that the Code required companies to prepare and certify detailed briefing material for representatives about each medicine which they would promote. The briefing material would be used to instruct representatives about the technical aspects of a medicine and how it should be promoted.

The Panel noted that the presentation at issue was an update on various Code and compliance issues. It did not directly or indirectly refer to a medicine or how it should be promoted. In the Panel's view, the Code did not require such material to be certified. The Panel thus ruled no breach of the Code. The Panel noted that the slides that were used were closely similar to the ones intended for use. Although it was unfortunate that the intended (and examined) slides had not been used, the Panel did not consider that high standards had not been maintained; no breach of the Code was ruled including no breach of Clause 2.

An anonymous, non contactable ex-employee submitted a complaint about training delivered at the Chiesi Limited sales conference in May 2015.

COMPLAINT

The complainant stated that a former colleague who had been at the sales conference, told him/her that, part way through a presentation, a trainer realised that the slides being projected were not those that had been approved. The trainer expressed his/her concerns directly to the audience that the slides were significantly different to those originally intended, then continued to deliver the remainder of this unapproved presentation.

The subject matter was compliance with the Code delivered by a senior manager who had reminded the audience of their ongoing obligations. The complainant's former colleague expressed empathy for the presenter but commented that the irony of the situation made it memorable and sales colleagues commented on this during the break after the presentation.

The complainant stated that he/she was more aware than his/her former colleague that using unapproved training materials was not permitted and a very serious matter. The complainant submitted that acting on the information outlined above, after it was shared with him/her in confidence, had been a difficult decision but the complainant believed that he/she was morally obliged to inform the PMCPA.

When responding to this complaint Chiesi was asked to bear in mind the requirements of Clauses 2, 9.1, 14.1 and 15.9 of the Code.

RESPONSE

Chiesi submitted that over the last few years it had made significant progress in its attitude and overall compliance structure. This was a continuous journey based on a solid compliance framework. Chiesi was committed to ensuring that all of its employees complied with the Code. Compliance as an objective, 'Succeeding the Right Way', was mandatory for all staff at every level.

The meeting in question was an internal Chiesi UK sales meeting held on 21 May 2015. The presenter in question was a senior manager, not a trainer, with a great deal of Code knowledge and experience who relied on the slides to simply facilitate the session.

The audience included UK sales representatives and the objective of the meeting was to update them on various company activities. The presentation in question was entitled 'Compliance Update – Succeeding the Right Way'. The objective of this 30-minute talk was to give the audience a compliance update and ensure they understood recent compliance activities in Chiesi. This was documented in the job bag summary. Chiesi submitted that the presentation therefore, *inter alia*, updated the audience on PMCPA audits at Chiesi and highlighted key dates for both transparency reporting and the 2016 Code. Chiesi submitted that the presentation was not on the technical aspects of any medicine nor did it direct the sales force on how to sell a medicine. Following guidance from a signatory and as per company procedures, the slides were examined using Zinc to ensure that the presentation was consistent in content with other presentations. Chiesi noted that the reviewer comments in Zinc were not relevant to this case as they related solely to the fact that the animated build within the powerpoint presentation could not be viewed in full by the reviewers checking the pdf.

Chiesi acknowledged that due to a miscommunication between the presenter and the staff member liaising with the speakers, the examined version of the slides was not provided to the AV production company. The slides used

were the original version sent to the AV production company in order for it to start preparing the master slide template.

Once on stage, at slide 3, the presenter realised that the slides projected were the original version. Chiesi noted that the slides used did not differ, in any meaningful way, to those that were examined, and made no difference at all to the objectives of this session and content of the presentation. With this in mind, and as author of both slide sets, in a professional and experienced manner, the presenter decided to continue. A document setting out the differences between the two versions was provided.

Chiesi submitted that as the intent and content of the slides at issue neither constituted training on a product nor instructions on how to sell a product, certification according to Clause 15.9 was not required and therefore there had been no breach in that regard. The slides were not promotional and did not require certification in accordance with Clause 14.1; thus there had been no breach of that clause. Given that there had been no breach of Clauses 14.1 or 15.9, the company had not failed to maintain high standards and, accordingly had not reduced confidence in the industry or brought it into disrepute. It therefore followed that Chiesi was not in breach of Clause 9.1 and accordingly Clause 2.

Chiesi was extremely disappointed that an ex-employee should report this to the PMCPA, given the worthy intent of the presentation.

To enhance the existing informal process and to prevent any issue arising from incorrect versions of slides being used at internal meetings, Chiesi had documented a process for managing slide presentations with written guidance and disseminated this to all those involved.

Chiesi believed that the Code neither required the presentation at issue to be certified nor examined, there was thus no case to answer. Nevertheless, Chiesi had given a clear explanation of the events that occurred and reassurance around the future use of slides at internal meetings, irrespective of whether the Code applied.

PANEL RULING

The Panel noted that Clause 15.9 of the Code required companies to prepare detailed briefing material for representatives on the technical aspects of each medicine which they would promote. Briefing material must comply with the relevant requirements of the Code and, in particular, was subject to the certification requirements of Clause 14. Briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The supplementary information to Clause 15.9 stated that the briefing material referred to in the clause consisted of both the training material used to instruct representatives about a medicine and the instructions given to them as to how the product should be promoted.

The Panel noted that the presentation at issue was an update on various Code and compliance issues. It did not directly or indirectly refer to a medicine or how it should be promoted. In the Panel's view, the Code did not require such material to be certified. The Panel thus ruled no breach of Clauses 14.1 and 15.9 of the Code. The Panel noted that the slides that were used were closely similar to the ones intended for use; they were not significantly different as stated by the complainant. Although it was unfortunate that the intended (and examined) slides had not been used, the Panel did not consider that high standards had not been maintained; no breach of Clause 9.1 was ruled. The Panel noted its rulings of no breach of the Code and further ruled no breach of Clause 2.

Complaint received **27 July 2015**

Case completed **20 August 2015**

CASE AUTH/2785/8/15

ANONYMOUS, NON-CONTACTABLE CONSULTANT v BAYER

Promotion of Eylea

An anonymous, non-contactable consultant complained about the promotion of Eylea (aflibercept) by Bayer plc. Lucentis (ranibizumab) to which the complainant referred, was marketed by Novartis Pharmaceuticals UK.

Eylea and Lucentis were intravitreal injections indicated, *inter alia*, for the treatment of neovascular (wet) age-related macular degeneration (wAMD) and visual impairment due to diabetic macular oedema (DMO) or due to macular oedema secondary to retinal vein occlusion.

The complainant stated he/she had discussed the treatment of patients with DMO, vein occlusion and wAMD with a Bayer representative and a head office employee several times over the past 18 months. These discussions centred around new trial data and included Protocol T, VIVID, VISTA, RISE and RIDE. The discussions were very informative, however the complainant stated that at a recent Novartis meeting it was explained that the data discussed with Bayer was off-licence in the UK.

The complainant was further concerned to learn that Protocol T was a head-to-head against an unlicensed dose of Lucentis. The complainant stated that the Bayer employees led him/her to believe that Eylea was superior to Lucentis, however they did not explain the dose difference or that it was unlicensed in the UK.

On understanding this difference the complainant raised it with the representative who stated there was no difference between the two doses of Lucentis and referred the complainant to a meeting to be held shortly in the area with a US retinal specialist to discuss Protocol T.

The complainant was concerned that other consultants would be similarly misled and that a forthcoming meeting would promote the unlicensed 0.3mg dose of Lucentis.

The detailed response from Bayer is given below.

The Panel noted that all of the studies cited by the complainant were DMO studies and that he/she appeared to be particularly concerned about the discussion of the Protocol T study as it involved an unlicensed dose of Lucentis.

The Panel was concerned that the complainant had very clearly referred to an 18 month period (ie from February 2014) in which he/she had discussed Eylea/Lucentis data and the treatment of patients with, *inter alia*, DMO with the Bayer representative and/or another employee. The complainant had not stated the context in which those discussions took place and did not refer to any promotional material which might have been used or any claims in particular to which he/she objected. In the Panel's view, it was most unlikely that discussions about DMO had taken place over such an extended period of time; Eylea was not licensed for use in DMO until August 2014 and the sales force was not issued with material until January 2015.

The Panel noted that the complainant also referred to discussions over the last 18 months about vein occlusion and wMAD. The complainant however bore the burden of proof and bearing in mind all the evidence, the Panel considered that the complainant had not established that any meetings or discussions had taken place between February 2014 and January 2015. No breaches of the Code were ruled.

The Panel noted that the e-detailer, available for use from January 2015, discussed the use of Eylea in visual impairment due to DMO and compared data from the RESTORE (Lucentis), VIVID/VISTA (Eylea) and RISE/RIDE (Lucentis), studies. Below tables of data, in small print, was the statement 'The dosing regimen for [Lucentis] used in the RESTORE, RISE and RIDE studies does not represent its current UK posology. For the current UK [Lucentis] posology, please refer to the [Lucentis] Summary of Product Characteristics'. The Panel did not consider that the page detailing the limitations of cross-over comparisons negated the misleading nature of the page in relation to the licensed dose of Lucentis as implied by Bayer. The Panel also noted that a subsequent slide described the design of the RESTORE and RISE/RIDE studies and referred to the unlicensed Lucentis dosing. The Panel noted Bayer's submission that although the 0.3mg dose of Lucentis was referred to on the slide about the study design of RISE/RIDE, the outcome data for this dose was not included. The Panel noted that the fact the results shown only related to the 0.5mg dose of Lucentis only became apparent if the representative 'tapped' on the study to reveal an additional dialogue box ie that information was not otherwise apparent to the reader and it appeared to be optional whether the representative revealed it or not. In addition the Panel noted that pages of the representatives' briefing material which expressed caution about the cross-study nature of the comparisons, were silent on the caution required about the reference to the unlicensed dose of Lucentis and the results. The Panel considered that given the content of the e-detailer and briefing material, the balance of probabilities was that since January 2015 the representative would have referred to the use of unlicensed doses of Lucentis

with customers. The implied comparison of Eylea with an unlicensed dose of Lucentis was misleading as alleged. Breaches of the Code were ruled. The Panel noted that the Lucentis studies cited in the e-detailer did not use the medicine as per the UK marketing authorization, but as Lucentis was marketed by Novartis then Bayer could not promote that product. No breach of the Code was ruled.

The Panel noted its comments above about the representatives' briefing material for the e-detailer. The Panel considered that to cite an unlicensed dose in the e-detailer and not to make the status of that dose clear in the briefing material and further fail to make it clear that the data discussed from RISE/RIDE related solely to the licensed dose was a significant omission which was likely to lead to representatives having discussions which were contrary to the Code. A breach of the Code was ruled.

The Panel noted its ruling of breaches of the Code above with regard to the e-detailer and the representatives' briefing material. In so much as a representative had used the material provided, the Panel ruled a breach of the Code.

With regard to possible discussions of Protocol T (which did not feature in the e-detailer), the Panel noted Bayer's submission that since the publication of the interim results in February 2015 there had been no sales calls recorded in the region in question where the representative and the head office employee had met with customers, nor any calls by the head office employee alone. The company thus could not identify the meetings in question. In any event, representatives had been briefed not to discuss the study proactively and to refer any unsolicited queries to medical information. The Panel did not consider that the complainant had shown that from February 2015, on the balance of probabilities and bearing in mind all of the evidence, that Bayer personnel had discussed and compared Lucentis and Eylea in the context of the Protocol T study as alleged. No breaches of the Code were ruled. There was no evidence that the representative had failed to maintain a high standard of ethical conduct. No breach of the Code was ruled. Whilst in the Panel's view it would have been preferable if the warning not to discuss the results proactively had appeared at the beginning of the briefing material, it did not consider that the Protocol T briefing material had advocated, either directly or indirectly, any course of action that would be likely to lead to a breach of the Code. On balance the Panel ruled no breach of the Code.

The Panel noted that the complainant was further concerned that a planned meeting would promote the unlicensed 0.3mg dose of Lucentis. The Panel presumed this was because the meeting would include discussion of the Protocol T study although the complainant had not been clear in this regard; it was not possible to contact him/her for further details. Bayer submitted that, on the information provided, the meeting appeared to be one of four which Bayer described as non-promotional about the work of a research network group. The Panel noted Bayer's submission that these meetings would discuss several studies including Protocol T. No speakers' slides had yet been submitted for its approval. The Panel noted that the invitation to one of the meetings described it as 'a scientific meet-the-expert session, exploring the latest updates from the [… research network group]'. The Panel noted Bayer's general submission about the likely considerable interest from UK ophthalmologists in the Protocol T data. In these circumstances and given Bayer's role and commercial interest, the Panel queried whether such meetings would be considered promotional. However, the complainant had made a very broad allegation about 'a forthcoming meeting' and no further details had been provided. In any event and as noted above, Lucentis was marketed by Novartis and in that regard a pharmaceutical company could not promote another company's medicine. No breach of the Code was ruled.

The Panel noted its rulings of breaches of the Code above with regard to the e-detailer and considered that Bayer had not maintained high standards. A breach of the Code was ruled. However the Panel did not consider that the rulings were such as to merit particular censure and in that regard no breach of Clause 2 was ruled.

An anonymous, non-contactable complainant who described themselves as a 'concerned consultant' complained about the promotion of Eylea (aflibercept) by Bayer plc. Lucentis (ranibizumab) to which the complainant referred, was marketed by Novartis Pharmaceuticals UK.

Eylea and Lucentis were intravitreal injections (ie into the eye). Both medicines were indicated, *inter alia*, for the treatment of neovascular (wet) age-related macular degeneration (wAMD) and visual impairment due to diabetic macular oedema (DMO) or due to macular oedema secondary to retinal vein occlusion.

COMPLAINT

The complainant stated that he/she had discussed the treatment of patients with DMO, vein occlusion and wAMD with a Bayer representative and a head office employee several times over the past 18 months. These discussions largely centred around new trials data from the diabetic retinopathy clinical research network group and included Protocol T, VIVID, VISTA, RISE and RIDE. The discussions were very informative, however the complainant stated that at a recent Novartis meeting, the chair, a well known professor in the complainant's region, explained that the data that he/she (the complainant) had been discussing with the Bayer representative was off-licence and off-label in the UK.

The complainant was further concerned to learn that Protocol T was a head-to-head against an unlicensed dose of Lucentis. The complainant stated that the Bayer employees led him/her to believe that Eylea was superior to Lucentis, however they did not explain the dose difference or that it was unlicensed in the UK.

On understanding this difference the complainant raised it with the representative who stated there was no difference between the two doses of Lucentis and referred the complainant to a meeting to be held shortly in the area with a US retinal specialist to discuss ProtocolT.

The complainant stated that he/she had always maintained a good relationship with the local representative and so preferred to remain anonymous, but was concerned that other consultants would also be misled in this way at the expense of patient care. The complainant was further concerned that a forthcoming meeting would promote the unlicensed 0.3mg dose of Lucentis.

When writing to Bayer, the Authority asked it to respond in relation to Clauses 2, 3.2, 7.2, 7.3, 9.1, 15.2 and 15.9 of the Code.

RESPONSE

Bayer stated that it took its responsibilities under the Code very seriously and as such, it undertook to ensure that all promotion in relation to Eylea was in line with its marketing authorization and those of any competitor products, comprised only accurate, fair and balanced communication of the scientific data and did not contain any misleading comparisons with other treatments. All personnel, including representatives, were regularly trained on the Code and were carefully briefed on how to manage unsolicited enquiries regarding unlicensed products. All off-label enquiries received by sales or marketing personnel were recorded on a request card and directed to the medical department for response. This procedure applied to all off-label enquires about prescription-only products in all indications.

Allegations of promotional activities relating to ProtocolT

Bayer submitted that ProtocolT was a randomised, controlled, US trial which compared Eylea, Lucentis and bevacizumab (Avastin) for the treatment of visual impairment due to DMO. The study was sponsored by the diabetic retinopathy clinical research network group, an independent, government-funded US research network which conducted research into a wide variety of treatments for diabetic eye disease. Bayer was not involved in the design or conduct of the study. ProtocolT used a 0.3mg dose of Lucentis which was approved in the US for the treatment of visual impairment due to DMO but was not the dose approved in the European marketing authorization (0.5mg); a posology of Eylea which differed from the exact wording of the summary of product characteristics (SPC) [2mg every four weeks vs 2mg every month]; and an intravitreal reformulation of Avastin which was not licensed for use anywhere in the world. The study was therefore inconsistent with the marketing authorizations of all three study medicines and so could not be included in any promotional material for Eylea nor discussed proactively by Bayer representatives. Unsolicited enquiries about ProtocolT were therefore handled exclusively by Bayer's medical department, as with all off-label enquiries.

The anonymous complainant referred to meetings with Bayer staff 'over the past 18 months' at which Eylea use in DMO and specific DMO studies were discussed, amongst other indications. This statement could not be correct as no Bayer representatives or other relevant personnel discussed any aspect of Eylea's use in visual impairment due to DMO in field-based customer visits before January 2015 – which was when sales materials for promotion in visual impairment due to DMO were first made available for use in the field – and no promotion of Eylea in DMO by any means occurred in the UK before September 2014. The marketing authorization for Eylea in visual impairment secondary to DMO was granted in August 2014, and although Bayer's sales team were trained and validated in this new indication by September 2014 in order to permit their presence on promotional stands carrying details of the new indication, Bayer did not release the DMO sales e-detailer to the team until January 2015.

In addition, the first full publication of interim 1 year results from ProtocolT only appeared online in February 2015 (Wells *et al* 2015), ie within 6 months of this complaint being received by the PMCPA. It was therefore not possible that the alleged ProtocolT discussions could have occurred with any Bayer staff over 18 months as claimed.

As ProtocolT was the first, and to date, only large, randomised, head-to-head comparison of the three anti-vascular endothelial growth factor (anti-VEGF) medicines used to treat DMO worldwide – Eylea, Lucentis and Avastin – Bayer knew that there would be considerable interest from UK ophthalmologists in these data when published and that it was highly likely that Bayer would receive unsolicited enquiries about the study and the outcomes for Eylea. For this reason, a comprehensive sales briefing document on ProtocolT covering its limitations and where the protocol deviated from the UK marketing authorizations of the study medicines, was certified and distributed to the sales and brand management team immediately after the paper was published in February 2015. The messages contained within were also reinforced through a conference call with the sales and marketing team. A copy of the briefing document was provided. Bayer submitted that this briefing gave clear instruction that the Lucentis 0.3mg dose was unlicensed and stated that Protocol T must therefore not be discussed proactively. All requests for reprints or further questions about ProtocolT must be documented and referred to medical information, which would respond to the customer and/or pass the request to the medical science liaison (MSL) team if more detailed discussion was required.

Bayer submitted that senior managers had interviewed the representative responsible for the region mentioned, and reviewed call records, which detailed any colleagues who had accompanied them on a call. All relevant head office staff had also been questioned by their senior manager about any meetings involving Bayer's representative in the area and/or customers in that area. Since the publication of ProtocolT, there had been no sales call recorded where the representative and the head office employee met with a customer in this region, and

also no calls made by the head office employee on customers where the representative was not present. Bayer had thus been unable to identify any meeting in the area where the alleged discussion between the complainant and the two Bayer employees might have occurred. Furthermore, Bayer's representative confirmed that he/she had always adhered to the briefing document and referred all unsolicited enquiries about ProtocolT to the medical department. Relevant head office staff likewise had confirmed that they did not engage in off-label discussion under any circumstances but always documented and then referred any unsolicited ProtocolT enquiries to the medical department for response. Sales/commercial personnel were not permitted to be present in the room when the MSL responded to customers' unsolicited off-label enquiries, and Bayer's medical director for ophthalmology confirmed with the MSL responsible for the region that there had been no deviations from this procedure.

Bayer was unable to comment on the Novartis-sponsored meeting reportedly attended by the complainant, at which ProtocolT appeared to have been discussed.

Alleged off-label promotional comparisons between Eylea and Lucentis

Copies of promotional material used by Bayer's sales team which compared Eylea and Lucentis in visual impairment secondary to DMO and/or was based upon the data/studies mentioned in the complaint were provided.

Bayer confirmed that the ProtocolT study was not mentioned in any promotional material for Eylea, for the reasons stated above, nor were there any comparisons of Eylea and Lucentis which quoted or otherwise referred to unlicensed doses of either medicine.

Bayer noted that the complainant had also referred to VIVID/VISTA and RISE/RIDE. VIVID and VISTA were the pivotal phase III studies for Eylea in DMO, where the sole comparator was macular laser photocoagulation, and RISE/RIDE were the equivalent studies for 0.3mg and 0.5mg Lucentis given monthly for two years vs placebo injection. For clarity, Bayer noted that the complainant implied that VIVID/VISTA and RISE/RIDE were also studies from the diabetic retinopathy clinical research network – this was not so. VIVID/VISTA (Eylea) and RISE/RIDE (Lucentis) were sponsored by the respective marketing authorization holders, whereas the diabetic retinopathy clinical research network was an independent, government-funded US research network.

The only promotional material which compared Eylea with Lucentis in DMO was a section of a DMO e-detailer, released to the sales team in January 2015. It contained only limited, qualitative cross-study comparisons of Eylea in the treatment of visual impairment due to DMO with trials of Lucentis, as in this indication there were no head-to-head data involving the licensed doses of both products. Certified briefing material for the sales team, which accompanied the e-detailer, made the limitations of such cross-study comparisons clear and required representatives to present the page describing these limitations to the health professional. Furthermore, the e-detailer was designed such that the slide presenting the limitations of the indirect comparison must be viewed before proceeding to any other part of the presentation.

In addition, the pivotal studies of Lucentis (RISE/RIDE) used a monthly dosing regimen of 0.5mg over 2 years. Monthly dosing was not inconsistent with the licensed posology of Lucentis (where monthly injection was mandated until maximum visual acuity was achieved and/or there were no signs of disease activity, with no maximum period of monthly dosing specified), but prolonged monthly dosing was not typical of the clinical use of Lucentis in the UK, where an 'as required' regimen with regular monitoring was more usual, nor did the regimen in RISE/RIDE reflect the full range of dosing options possible within the current Lucentis SPC. Advice to this effect, and a recommendation to consult the current Lucentis SPC, was therefore always included in promotional materials which quoted RISE and RIDE.

For completeness and accuracy, Bayer highlighted that the 0.3mg dose of Lucentis was briefly mentioned on the slide about the study design of RISE/RIDE, but the outcome data for this dose were not included and there was no attempt to compare this dose with Eylea. Most of the qualitative comparison pages in the e-detailer related to RESTORE, a study not mentioned by the complainant, which used an 'as required' posology of 0.5mg Lucentis corresponding most closely of all published Lucentis studies to real-life UK clinical usage; this study was also referenced by the National Institute for Health and Care Excellence (NICE) for the same purpose, in the single technology appraisal of Eylea in DMO.

In addition, there was a leavepiece, promotional stand video and a supplement all of which referred to studies mentioned by the complainant, excepting ProtocolT. These did not include any mention of off-label doses or any comparison between products.

Planned Bayer-sponsored meetings

Bayer submitted that the meeting referenced in the complaint was one in a series of four non-promotional, scientific meetings due to be held in late September 2015 at different geographic locations. Bayer could not be certain from the complaint of the specific meeting at issue, but all four were similar in scope. These meetings were not 'ProtocolT' meetings nor Eylea promotional meetings, but were scientific, non-promotional meetings about the work of the diabetic retinopathy clinical research network group, and topics would include discussion of several different studies, for example, Protocol S which compared Lucentis to prompt or deferred pan-retinal photocoagulation. As previously stated, the diabetic retinopathy clinical research network group was a highly regarded,

independent, government-funded US research network which conducted research into a wide variety of medical and non-medical treatments for diabetic eye disease. The two speakers were recognised as world-class researchers in this field. UK clinicians were genuinely interested in the breadth of the research sponsored by the group and enthusiastic to learn how the network was organised to maximise the efficiency of study conduct and how these learnings might be applied within the UK.

These non-promotional, scientific meetings were managed by the medical team. The sales team would not attend them, would not distribute invitations (which would be done via the medical department and/or the local meeting chair) and there would be no promotional stand or other promotional activities linked to the meetings. The only external materials available at present were the invitations and template covering emails for delegates and chairs of the meetings, all of which had been approved and certified. There was also an internal concept document, which provided more information about the objectives and proposed content of the meetings.

There were currently no slides available for the meetings, as these were still being prepared by the speakers. The meeting content, any further external materials relating to the meetings and all other relevant arrangements would, in due course, be certified as required by the Code before the first meeting was held.

Summary

In summary, with regard to Clause 3.2, Bayer submitted that it had taken every step necessary to ensure Eylea was promoted only within its marketing authorization and in line with its SPC. The company recognised that ProtocolT used products with dosage/posology/formulation outside their marketing authorizations, the representatives had been briefed accordingly to document and refer all unsolicited enquiries to the medical department. Bayer had never used data from ProtocolT promotionally. The meetings planned for late September were non-promotional, scientific exchange meetings with a balanced, educational agenda that had wide relevance for clinicians interested in research and treatment in diabetic eye disease; the meetings were neither focussed on studies involving Eylea nor designed to promote Eylea, and the sales team was not involved in them in any way. Bayer thus denied a breach of Clause 3.2.

With regard to Clauses 7.2 and 7.3, no promotional material, about the use of Lucentis vs Eylea in visual impairment secondary to DMO, included comparisons based on, or referred to, ProtocolT; nor had any other comparisons been made which involved unlicensed doses of either medicine. Bayer therefore denied any breach of the Code in relation to inappropriate or off-licence promotional claims and/or comparisons.

With regard to Clauses 15.2 and 15.9, Bayer submitted its sales team was always fully briefed on any relevant new data, and such briefings were certified under the Code. For ProtocolT, the briefings clearly stated that the dose of Lucentis used was off-label and that the study must not be proactively discussed under any circumstances. Interviews with the representative concerned and relevant head office staff, and scrutiny of the call records for the relevant territory, had failed to produce any evidence to support the allegations by the anonymous complainant that Bayer employees failed to follow the approved procedures. In addition, the call records did not support that any meeting occurred in the relevant territory which might correspond to the meeting alleged by the complainant. In line with Bayer policy, representatives were never present at customer visits when medical department personnel responded to any off-label enquiry.

PANEL RULING

The Panel noted that the complainant was anonymous. As stated in the introduction to the Constitution and Procedure, such complaints were accepted and like all complaints, judged on the evidence provided by both parties. Complainants had the burden of proving their complaint on the balance of probabilities. The complainant had neither referred to any specific material or claim nor provided any material to substantiate his/her allegations. As the complainant was non-contactable it was not possible to ask him/her for further information.

The Panel noted the complainant's allegation that he/she had had several discussions over the past 18 months [ie since February 2014] with a representative and another Bayer employee about the treatment of patients with diabetic macular oedema (DMO), vein occlusion and (wet) age-related macular degeneration (wAMD). The complainant submitted that the discussions had largely centred around new trial data from the diabetic retinopathy clinical research network group and included ProtocolT, VIVID, VISTA, RISE and RIDE. The complainant found the discussions very informative but was concerned that the data he/she had discussed with the Bayer representative was off-licence and off-label in the UK. The complainant appeared to be particularly concerned about the discussion of the ProtocolT study as it involved an unlicensed dose of Lucentis. The Panel noted that all of the studies cited by the complainant were DMO studies.

The Panel noted Bayer's submission that none of its representatives or other relevant personnel had discussed any aspect of Eylea use in visual impairment due to DMO in field-based customer visits before January 2015 when sales materials for promotion in visual impairment due to DMO were first made available; no promotion of Eylea in DMO by any means occurred in the UK before September 2014; the marketing authorization for Eylea in visual impairment secondary to DMO was not granted until August 2014. Although Bayer had submitted that its sales team was trained and validated in this new indication by September 2014, in order to permit their presence on promotional stands carrying details of the new indication, the DMO sales e-detailer was not released until January 2015.

The Panel was concerned that the complainant had very clearly referred to an 18 month period (ie from February 2014) in which he/she had discussed Eylea/Lucentis data and the treatment of patients with, *inter alia*, DMO with the Bayer representative and/or another employee. The complainant had not stated the context in which those discussions took place and did not refer to any promotional material which might have been used or any claims in particular to which he/she objected. In the Panel's view, given Bayer's submission it was most unlikely that discussions about DMO had taken place over such an extended period of time. Eylea was not licensed for use in DMO until August 2014 and the sales force was not issued with material (an e-detailer) to use in the field until January 2015.

Given the 18 month time period referred to by the complainant and Bayer's submissions regarding the dates when material was released to the representatives, the Panel had some concerns about the robustness of the complaint. Nonetheless, the Panel noted that the complainant referred to discussions over the last 18 months not only about DMO but also about vein occlusion and wMAD. The complainant however bore the burden of proof and bearing in mind all the evidence, the Panel considered that the complainant had not established that any meetings or discussions had taken place between February 2014 and January 2015. No breach of Clauses 3.2, 7.2 and 7.3 were ruled.

The Panel noted that the e-detailer provider provided by Bayer (available for use from January 2015) discussed the use of Eylea in visual impairment due to DMO and presented, in tabular form, a comparison of data from the RESTORE (Lucentis, 0.5mg/month for 3 months and then as required), VIVID/VISTA (Eylea) and RISE/RIDE (Lucentis, 0.3mg or 0.5mg monthly) studies. Below the tables of data, in small print, was the statement 'The dosing regimen for [Lucentis] used in the RESTORE, RISE and RIDE studies does not represent its current UK posology. For the current UK [Lucentis] posology, please refer to the [Lucentis] Summary of Product Characteristics'. The Panel noted that the supplementary information to Clause 7.2 stated that in general, claims should not be qualified by the use of footnotes and the like. The Panel did not consider that the page detailing the limitations of cross-over comparisons negated the misleading nature of the page in relation to the licensed dose of Lucentis as implied by Bayer. The Panel also noted that a subsequent slide described the design of the RESTORE and RISE/RIDE studies and referred to the unlicensed Lucentis dosing. The Panel noted Bayer's submission that although the 0.3mg dose of Lucentis was referred to on the slide about the study design of RISE/RIDE, the outcome data for this dose was not included. The Panel noted that the fact the results shown only related to the 0.5mg dose of Lucentis only became apparent if the representative 'tapped' on the study to reveal an additional dialogue box ie that information was not otherwise apparent to the reader and it appeared to be optional whether the representative revealed it or not. In addition the Panel noted that those pages of the representatives' briefing material provided by Bayer expressed caution about the cross-study nature of the comparisons but were silent on the caution required in relation to the reference to the unlicensed dose of Lucentis and the results. The Panel considered that given the content of the e-detailer and briefing material, the balance of probabilities was that since January 2015 the representative would have referred to the use of unlicensed doses of Lucentis with customers. The implied comparison of Eylea with an unlicensed dose of Lucentis was misleading as alleged. A breach of Clause 7.2 and 7.3 was ruled. The Panel noted that Clause 3.2 required the promotion of a medicine to be in accordance with the particulars listed in its SPC. The definition of promotion given in Clause 1.2 related, *inter alia*, to an activity undertaken by a pharmaceutical company, which promoted the administration, consumption, prescription, purchase, recommendation, sale or supply of *its* medicines (emphasis added). The Lucentis studies cited in the e-detailer did not use the medicine as per the UK marketing authorization, but as Lucentis was marketed by Novartis then Bayer could not promote that product. No breach of Clause 3.2 was ruled.

The Panel noted its comments above about the representatives' briefing material for the e-detailer. The Panel considered that to cite an unlicensed dose in the e-detailer and then not to make the status of that dose clear in the briefing material and further fail to make it clear that the data discussed from RISE/RIDE related solely to the licensed dose was a significant omission which was likely to lead to representatives having discussions which were contrary to the Code. A breach of Clause 15.9 was ruled in relation to the briefing material for the e-detailer.

The Panel noted its ruling of breaches of the Code above with regard to the e-detailer and the representatives' briefing material. In so much as a representative had used the material provided, the Panel ruled a breach of Clause 15.2.

With regard to possible discussions of Protocol T (which did not feature in the e-detailer), the Panel noted Bayer's submission that since the publication of the first interim results from Protocol T in February 2015 (Wells *et al*) there had been no sales calls recorded in the region in question where the representative and a head office employee had met with customers, nor any calls by the head office employee alone. The company thus could not identify the meetings in question. In any event, representatives had been briefed immediately after publication of Wells *et al* not to discuss the study proactively and to refer any unsolicited queries to medical information; the representative in question had confirmed that this indeed was what he/she had always done. The Panel did not consider that the complainant had shown that from February 2015, on the balance of probabilities and bearing in mind all of the evidence, Bayer personnel had discussed and compared Lucentis and Eylea in the context of the Protocol T study as alleged. No breach of Clauses 3.2, 7.2 and 7.3 were ruled. There was no evidence that the representative had failed to maintain a high standard of ethical conduct. No breach of

Clause 15.2 was ruled. Whilst in the Panel's view it would have been preferable if the warning not to discuss the results proactively had appeared at the beginning of the briefing material, it did not consider that the Protocol T briefing material had advocated, either directly or indirectly, any course of action that would be likely to lead to a breach of the Code. On balance the Panel ruled no breach of Clause 15.9.

The Panel noted that the complainant was further concerned that there was a meeting planned that would promote the unlicensed 0.3mg dose of Lucentis. The Panel presumed this was because the meeting would include discussion of the Protocol T study although the complainant had not been clear in this regard; it was not possible to contact him/her for further details. Bayer had submitted that, on the information provided, the meeting appeared to be one of four which Bayer described as non-promotional about the work of the diabetic retinopathy clinical research network group. The Panel noted Bayer's submission that these meetings would discuss several studies including Protocol T. No speakers' slides had yet been submitted for its approval. The Panel noted that the invitation to one of the meetings described it as 'a scientific meet-the-expert session, exploring the latest updates from the [diabetic retinopathy clinical research network group]'. The Panel noted Bayer's general submission about the likely considerable interest from UK ophthalmologists in the Protocol T data. In these circumstances and given Bayer's role and commercial interest, the Panel queried whether such meetings would be considered promotional. However, the complainant had made a very broad allegation about 'a forthcoming meeting' and no further details had been provided. In any event and as noted above, Lucentis was marketed by Novartis and in that regard a pharmaceutical company could not promote another company's medicine. No breach of Clause 3.2 was ruled.

The Panel noted its ruling of a breach of Clauses 7.2, 7.3 and 15.9 above with regard to the e-detailer and considered that Bayer had not maintained high standards. A breach of Clause 9.1 was ruled. However the Panel did not consider that the rulings were such as to merit particular censure and in that regard no breach of Clause 2 was ruled.

Complaint received **3 August 2015**

Case completed **20 October 2015**

INFORMATION PHARMACIST v UCB

Keppra information on a nurses' website

An NHS medicines information pharmacist complained about information about Keppra (levetiracetam) on the Epilepsy Nurse Association (ESNA) website. The information was headed 'Data on Keppra v generic levetiracetam' and reproduced an email, the first paragraph of which stated 'Thank you for your request for information on the prescribing of branded Keppra (levetiracetam) vs. generic levetiracetam …'. The letter was 'signed' by a medical information officer and a telephone number for further information was given. Keppra was marketed by UCB Pharma and was indicated for epilepsy.

The complainant queried whether it was appropriate and ethical for a company piece to be posted on an apparently independent website without being identified as such. It was only by cross-checking the telephone number that the source [ie UCB] was apparent. The material had been prepared by UCB's medical information department but was not credited to the company.

The detailed response from UCB is given below.

The Panel noted UCB's submission that the material was published without its knowledge or consent. It appeared that a UCB medical information response to what appeared to be an unsolicited enquiry from an epilepsy nurse in 2012 had been published by ENSA on its own website. The Panel noted that the request for information was originally sent to a UCB colleague who forwarded it to the author for reply. It appeared that the health professional and original UCB recipient had, at the very least, been in contact previously. It was not known whether the health professional had links with ESNA and/or intended to publish the response nor was it known whether the original UCB recipient knew of any such link/ intention. However, the original recipient described the email as a medical information request from an epilepsy nurse specialist. Following a request from UCB, ENSA removed the material from its website.

The Panel considered that given the circumstances, UCB was not responsible for the publication of the information at issue and thus neither prescribing information nor a statement identifying the responsible pharmaceutical company were required. No breaches of the Code were ruled.

An NHS medicines information pharmacist complained about information he had seen about Keppra (levetiracetam) on the news page of the Epilepsy Nurse Association (ESNA) website. Keppra was marketed by UCB Pharma Ltd and was indicated for epilepsy. The information on the ESNA website was headed 'Data on Keppra v generic levetiracetam' and reproduced the body of an email, the first paragraph of which stated 'Thank you for your request for information on the prescribing of branded Keppra (levetiracetam) vs. generic levetiracetam …'. The letter was 'signed' by a medical information officer and a telephone number for further information was given.

COMPLAINT

The complainant queried whether it was appropriate for a company piece to be posted on an apparently independent website without being identified as such. The complainant noted that it was only by cross-checking the telephone number that the source of the document [ie UCB] was apparent. The complainant noted that the material at issue had been prepared by UCB's medical information department but was not credited to the company. The complainant did not consider that such conduct was ethical.

When writing to UCB, the Authority asked it to consider the requirements of Clauses 4.1, 9.1 and 9.10 of the Code.

RESPONSE

UCB submitted that its records indicated that when the advice was given the medical information officer whose name appeared on the website text in question worked in the medical information team responding to unsolicited medical information queries on Keppra and generic versions. Based on the similarity of the text in UCB's medical information email response and that which appeared on the website, the text in question stemmed from an unsolicited email request for medical information from an epilepsy nurse specialist in March 2012, on switching from Keppra to generic levetiracetam. The medical information team responded the day after receiving the request. It appeared that, unknown to UCB, text from that response was subsequently extracted and published on the ESNA website without UCB's consent. The published extract from the medical information response was then read by the complainant and formed the basis of this complaint.

UCB noted that Clause 4.1 dealt with the provision of prescribing information in promotional materials. However, Clause 1.2 specifically excluded, replies made in response to individual enquires from members of the health professions from the definition of promotion. As UCB's response to an unsolicited medical information request, as evidenced by the opening statement of the text from the ESNA website and further evidenced by the job title of the responding UCB team member, fell within the exemption to Clause 1.2, UCB submitted that the email did not require prescribing information and so it denied a breach of Clause 4.1.

UCB further noted that the supplementary information to Clause 14.3 excluded written responses from medical information departments from the certification requirements. As such, the medical information response in March 2012 was not certified.

UCB noted that Clause 9.10 stated that materials relating to medicines and their uses, whether promotional or not, and information relating to human health or diseases which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company.

UCB stated that its response to the medical information request was sent via the company's email address and the medical information officer was clearly identified as such. Since the requester received the response the day after submitting the request to UCB, the company strongly believed that he/she was fully aware that the response was from UCB. Furthermore, UCB was not aware that the response had been extracted and posted on the ESNA website and it did not sponsor the content of this site. UCB denied a breach of Clause 9.10.

UCB noted that its response to the epilepsy nurse specialist was made in a timely manner, it was accurate at the time, did not mislead and was not promotional. The medical information officer was clearly identified and the email response was sent using UCB's email address. UCB submitted that it had maintained high standards and hence had not breached Clause 9.1.

UCB explained that on an average, it responded to between 400-500 medical information queries each month in the UK. In responding to such enquiries, it strove to adhere to compliance and other requirements as stipulated by the Code. This complaint had arisen because a medical information response addressed to an individual health professional had been published on an external website without the company's prior knowledge and consent.

UCB stated that it continued to review its processes to ensure the highest standards and since 2012, it included the following in all its responses: 'Please note that the attached literature is for your own personal use, and due to copyright may not be forwarded'. Although UCB firmly believed it was not in breach of the Code for the reasons stated above, based on this case, it had updated the statement, to read: 'Please note that UCB's response and any attached literature are for your own personal use, and due to copyright may not be forwarded/ published'. Further, emailed responses were now sent as a pdf, instead of free text.

UCB noted that when it was notified of this complaint it contacted ESNA and asked it to remove the text in question from its website.

Based on the above, UCB contended that it would be unfair to rule it in breach of the Code for actions undertaken without its prior knowledge and consent. Although UCB firmly believed it was not in breach of the Code as set out above, the additional actions undertaken after the receipt of the complaint strongly indicated that it always strove to maintain the highest standards.

PANEL RULING

The Panel noted that the epilepsy nurse specialist's email in March 2012 asked for information or published papers on switching from Keppra to the generic version and noted that in one study 40% changed back to Keppra. In the Panel's view the email appeared to be an unsolicited request for medical information.

The Panel noted the supplementary information to Clause 1.2 Replies Intended for Use in Response to Individual Enquiries which stated, *inter alia*:

> 'The exemption to the definition of promotion for replies made in response to individual enquiries from members of the health professions or other relevant decision makers relates to unsolicited enquiries only. An unsolicited enquiry is one without any prompting from the company.'

The supplementary information to Clause 14.3 Examination of Other Material made it clear that such material did not need to be certified under Clause 14.

The Panel noted UCB's submission that the material on the ESNA website was published without UCB's knowledge or consent. It appeared that a UCB medical information response to what appeared to be an unsolicited enquiry in 2012 had been published by ENSA on its own website. The Panel noted that the request for information was originally sent not to the author of the response but to a UCB colleague who forwarded it to the author for reply. It appeared that the epilepsy nurse specialist and original UCB recipient had, at the very least, been in contact previously. It was not known whether the nurse had links with ESNA and/or intended to publish the response nor was it known whether the original UCB recipient knew of any such link/intention. However, the original recipient described the email as a medical information request from a health professional. Following a request from UCB, ENSA removed the material from its website.

The Panel considered that given the circumstances, UCB was not responsible for the publication of the information at issue and thus neither prescribing information nor a statement identifying the responsible pharmaceutical company were required. It ruled no breach of Clause 9.10. The Panel also ruled no breach of Clause 9.1 as UCB had not failed to maintain high standards. The Panel also ruled no breach of Clause 4.1 as there was not a specific allegation about the lack of prescribing information.

Complaint received **6 August 2015**

Case completed **7 September 2015**

CASE AUTH/2787/8/15

VOLUNTARY ADMISSION BY GLAXOSMITHKLINE

Online advertisements for Incruse and Relvar

GlaxoSmithKline voluntarily admitted that some online advertisements for Incruse Ellipta (umeclidinium bromide) plus Relvar Ellipta (fluticasone furoate and vilanterol trifenatate) were in breach of the Code. Relvar and Incruse could be used together in chronic obstructive pulmonary disease (COPD).

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 GlaxoSmithKline.

GlaxoSmithKline explained that it noted an advertisement on the Pulse website had a blurry non-proprietary name and only linked to the Incruse prescribing information. Two other advertisements had similar issues. On checking it was found that the final form of some advertisements had not been certified as the signatories had not seen the final form. All online advertisements for Incruse plus Relvar were removed and two further items were found with similar issues. Preventative actions had commenced with a voluntary admission to the PMCPA.

GlaxoSmithKline explained that from January 2015 it had promoted Incruse and Relvar together for patients for COPD; the medicines had previously been advertised separately. Advertising space planned originally for Incruse alone was assigned to Incruse plus Relvar. However the media plan continued to refer to 'Incruse' rather than 'Incruse + Relvar'.

GlaxoSmithKline noted that though one of the advertisements was stamped 'Amend and Progress' in ZINC, it was inadvertently sent to the company's media agency for publication in the belief that it had been certified. A second advertisement was released to the Nursing Times, signed only by one signatory.

GlaxoSmithKline's investigation showed that of seven job bags, a further two failed to meet the standards required by the Code. Of the five items published online, three were released before certification. Additionally, all five had a degree of illegibility and incomplete prescribing information from 20 April to 2 July.

GlaxoSmithKline explained that over a space of three weeks over Easter 2015, those working on the Incruse and Relvar advertisements had changed roles and responsibilities and the digital advertising plan, workload priorities and resources were reconsidered.

With regard to the prescribing information, GlaxoSmithKline explained that at certification and when all advertisements were published online a direct link for dual prescribing information was made available. However, the link broke and the media agency asked GlaxoSmithKline for replacement prescribing information 'for Incruse' (rather than for Incruse plus Relvar). Consequently, from 20 April until 2 July the five online advertisements only linked to Incruse prescribing information and not to the prescribing information for both medicines.

With regard to items being released before certification, GlaxoSmithKline stated that this error was likely to have been the result of a misread code for a similar certified item resulting in misidentification. Further, misinterpretation of a message might also have been either causal or contributory. Though released in good faith the item was, unfortunately, released in error in breach of the Code.

GlaxoSmithKline admitted that high standards had not been maintained.

Further details from GlaxoSmithKline are given below.

The Panel noted the three specific compliance issues with five digital advertisements for Incruse plus Relvar: poor legibility of the non-proprietary names, omission of prescribing information for Relvar and publication prior to certification. The poor legibility of the non-proprietary names and the omission of the Relvar prescribing information affected all five of the advertisements and three of the five advertisements were published before certification.

The Panel noted all five of the online advertisements for Incruse plus Relvar only linked to the prescribing information for Incruse. As the prescribing information for Relvar was not available via the link a breach of the Code was ruled as acknowledged by GlaxoSmithKline.

The Panel noted that although the advertisements at issue included the non-proprietary names in the correct position, the names were not readily readable. A breach of the Code was ruled as acknowledged by GlaxoSmithKline.

The Panel noted that three of the advertisements at issue had been published online before final certification. A breach of the Code was ruled as acknowledged by GlaxoSmithKline.

The Panel noted that the Code required promotional material on the Internet directed to a UK audience to comply with the Code. The Panel noted its rulings of breaches of the Code above and thus ruled a breach of the Code as acknowledged by

GlaxoSmithKline.

No evidence had been provided to the Panel to demonstrate that relevant personnel had not been trained. On balance the Panel ruled no breach of the Code.

Overall, the Panel considered that high standards had not been maintained. A breach of the Code was ruled as acknowledged by GlaxoSmithKline.

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

GlaxoSmithKline voluntarily admitted that a number of digital advertisements for Incruse Ellipta (umeclidinium bromide) plus Relvar Ellipta (fluticasone furoate and vilanterol trifenatate) were published online without meeting the requirements of the 2015 Code.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with GlaxoSmithKline.

On 2 July 2015 a GlaxoSmithKline a senior employee saw an advertisement on the Pulse website with a blurry non-proprietary name, clicked through to the prescribing information and noticed that only the Incruse prescribing information was available. Two other advertisements had similar issues. The employee then checked the ZINC job bag and found that for some, final certification had not occurred as the final form had not been viewed and the signatories had been waiting for this. After escalating this issue to senior management, all online advertisements for Incruse plus Relvar were removed the same day. An investigation commenced and a further two items were found with similar issues and an understanding as to the circumstances had been documented. Preventative actions had commenced with a voluntary admission to the PMCPA.

VOLUNTARY ADMISSION

GlaxoSmithKline stated that Incruse was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD). Relvar was available in two strengths for asthma; the lower dose (92/22) was also indicated for symptomatic treatment of adults with COPD with a FEV1 <70% predicted normal (post bronchodilator) with an exacerbation history despite regular bronchodilator therapy. Relvar and Incruse could be used together in COPD. As there were three active ingredients this was sometimes termed 'triple therapy'.

In January 2015 it was decided to promote Incruse and Relvar together for patients for COPD; the medicines had previously been advertised separately. Advertising space that was planned originally for Incruse alone was assigned to Incruse plus Relvar. However, in spite of this change, the media plan continued to refer to 'Incruse' rather than the more precise and accurate descriptor of 'Incruse + Relvar'. The intention had been to create 32 advertisements for publication in 13 online journals over the course of 2015. During February and March a junior employee was assigned to work on 13 advertisements for publication in Nursing Times, Nursing in Practice, GP online and Pulse.

The senior employee saw a banner advertisement (ref UK/FFT/0030/15a) coincidentally on 2 July in the online edition of Pulse. The advertisement had been certified in its final form via an appropriate staging link on 16 March 2015, however a degree of blurring particularly affecting the non-proprietary names was noted. This was not how the senior employee recalled seeing the item in March. Moreover, it was noted that the URL to the prescribing information linked to the Incruse prescribing information only. This was both confusing and concerning as, when examined on staging, the advertisement had linked correctly to prescribing information for both medicines. Furthermore, the senior employee recalled that the copy was fully legible at the certification stage. As a result the senior employee decided to look further at this and other related items in ZINC.

It became apparent from reviewing the item and a further two items that all three were similarly affected from a legibility point of view. There were also issues of certification with these two items.

UK/FFT/0032/15 had not been certified in its final form. At the certification stage (17 March), the two signatories noted that the staging link failed and the item could not be visualised in its final form; the advertisement thus could not be certified as intended on that date. Though stamped 'Amend and Progress' in ZINC, a junior employee inadvertently released the advertisement to the media agency for publication the following day believing that it had been certified as scheduled the day before.

UK/FFT/0032/15a had been released to the Nursing Times signed by only one signatory.

Having appropriately checked the initial advertisement and the further two advertisements identified, the senior employee alerted marketing colleagues to his findings. These were then escalated to the relevant medical and commercial directors as a priority.

The media agency was promptly instructed to recall the online digital advertising for Incruse plus Relvar with the result that all online advertisements were taken down on 2 July and the deviations reported to the relevant internal governance committee. An investigation was initiated immediately to ascertain how and why such discrepancies could have occurred following the advertisements' online appearance in various digital publications.

<u>Investigation findings</u>

The investigation provided a full review of all digital

advertising items created for Incruse plus Relvar during quarter 1 2015. Of seven job bags, a further two items were identified as failing to meet the standards required by the Code and details were provided.

GlaxoSmithKline submitted that of five items fully progressed and published online, three were released before certification. Additionally, all five items demonstrated a degree of illegibility and incomplete prescribing information from 20 April to 2 July.

Text resolution and legibility considerations: on 23 March a senior employee noticed that the non-proprietary names for Incruse and Relvar were not as clear as they might be on the live site. This had not been a feature when seen at staging. Before changing roles, the junior employee contacted the media agency and the company's design team to put on hold any further advertisements that were being developed at that time. The design team worked to enhance resolution and update the images.

On 27 March the junior employee took up a different role in a different location within GlaxoSmithKline. The digital advertising plan was handed over to colleagues who decided to pause until after Easter when further consideration could be given to capacity to deliver the plan. At that stage it was not clearly understood that some items were being re-worked by the design team.

On 13 April the plan, workload priorities and resources were duly reconsidered by the marketing team. The decision to do no additional advertising in quarter 2 was confirmed. As a consequence, no new advertisements were created and pending items not yet approved were cancelled.

Prescribing information considerations: on 9 March GlaxoSmithKline sent the prescribing information URL to its media agency as a prelude to online publication of the digital advertisements being progressed through ZINC. The URL linked to a 'dual PI' pdf document created specifically for the Incruse plus Relvar advertisements and certified as a separate item in its own right.

At certification and when all advertisements were published in the various online journals, this direct link made prescribing information available for both Incruse and Relvar within each item as required by the Code. However the URL to the prescribing information broke and on 20 April the agency asked for replacement prescribing information 'for Incruse' (rather than for Incruse plus Relvar) with the result that from 20 April until 2 July, the replacement link in the five advertisements only linked to prescribing information for Incruse alone and not, as intended and as certified, to the prescribing information for both medicines.

Release prior to certification: The investigation had shown that this error was likely to have been the result of one, or possibly two, causes. Firstly, a misreading of the item's ZINC code for a similar certified item might have resulted in misidentification. Secondly, misinterpretation of a ZINC message might also have been either causal or contributory; the notification read, 'This job has completed its circulation and was passed to you by [the named signatory]'. The same notification was generated regardless of the outcome of a review or a certification cycle. In this case, there had been no reason to doubt that such a straightforward item would not have been certified as scheduled. Though released in good faith the item was, unfortunately, released in error thereby breaching Clauses 4.1, 4.2, 4.3, 4.4, 14.1, 16.1 and 28.1 of the Code.

GlaxoSmithKline admitted that as a result of the investigation, high standards had not been maintained in breach of Clause 9.1.

GlaxoSmithKline stated that a number of preventative actions had been initiated, including re-training of the team in the requirements of the Code, a review of the interface with digital agencies and a review of current promotional materials.

When writing to confirm that the matter would be taken up under the Code, the Authority asked GlaxoSmithKline to provide any further comments it might have in relation to Clause 2.

RESPONSE

GlaxoSmithKline confirmed that with respect to Clauses 4.1, 4.2, 4.3, 4.4, 9.1, 16.1 and 28.1 it had no further comments to add to those detailed previously.

However, with respect to Clause 2, GlaxoSmithKline acknowledged that whilst high standards were not maintained at all times, it noted that Clause 2 was retained for circumstances that warranted particular censure. It submitted that neither patient nor public health had been prejudiced by the above breaches, nor was there risk of inducement or pre-authorization promotion.

GlaxoSmithKline stated it had actively initiated a comprehensive preventative programme to address the issues highlighted during the investigation of this case. These activities included:

1 A statement to the organisation on 13 August to highlight the need to maintain the highest of standards and comply fully with both the GlaxoSmithKline internal governance framework and the Code.

2 A review (completed 21 August) of current digital advertising materials across all therapy teams.

3 Two senior managers presented on the recent voluntary admissions to the PMCPA to the UK respiratory team at a meeting on 26 August.

4 A further briefing on the case together with updates to ongoing CAPA (corrective actions, preventative actions) related to digital advertising would be rolled out to individual therapy brand teams within the respiratory therapeutic area by the end of August 2015.

5 When the case was concluded with the PMCPA, it would be presented in detail at an internal GlaxoSmithKline Code Forum meeting (anticipated October 2015).

6 It was planned to conclude detailed re-training on the requirements of the Code by November 2015 across all the in house therapy teams.

7 A comprehensive review of the interfaces between GlaxoSmithKline and its various digital agencies had been initiated and was scheduled for completion in November 2015.

With respect to the differences in legibility between the certified advertisements and those that appeared online, the scientific name of the product was illegible due to blurring. The company had taken a deeper look at the technical specifications required. The advertisements did not seem to fully meet the technical specification which could result in distortion. Some of the differences in pixels were small and what difference they would make was unclear. Further investigation was ongoing.

As part of the comprehensive review (point 7 above), GlaxoSmithKline had shared information on the deviation with the agency and agreed to hold regular teleconferences to monitor progress against agreed actions. Such actions included, but were not limited to, enhanced quality control checks, review on different browsers and devices and reiteration of the importance of publishing only certified material.

GlaxoSmithKline explained that the term 'staging site' described a website used to review and test new content or functionality. The staging site was a mirror image of the 'live site' to ensure content could be displayed in its final form before being released on the live site (technically referred to as the Production Site). The staging site was held securely behind a login to ensure that content that did not pass testing could not be viewed.

It was common practice in web design and content creation for organisations to have three distinctly separate areas of a website, namely, the development environment, where hardware or software was created, the staging environment, where there was review and testing and finally a release or publishing to the live production environment.

GlaxoSmithKline submitted that it operated a standardized process for the review and approval of all digital material, whether on its own web assets or via a third party. When the material had been reviewed in ZINC, it moved to the development environment. Once creation was complete the final version was passed to the staging site and a screen shot and link to the staging environment was passed to signatories for review and final certification. This enabled the review of the static screen shot and the built version so as to test links, functionality of dynamic content etc., exactly as it would appear on the live site. Once the certificate had been received by the originator, the item was published.

PANEL RULING

The Panel noted GlaxoSmithKline had identified three specific compliance issues with five digital advertisements for Incruse plus Relvar: poor legibility of the non-proprietary names, omission of prescribing information for Relvar and publication prior to certification. The poor legibility of the non-proprietary names and the omission of the Relvar prescribing information affected all five of the advertisements and three of the five advertisements were published before certification.

The Panel noted all five of the online advertisements for Incruse plus Relvar were promotional; however the link to the prescribing information only provided prescribing information for Incruse. The prescribing information for Relvar was not available via the link as required. In that regard, the Panel noted that when it was decided to advertise the two medicines together there had been a failure to correctly reassign the advertisements from 'Incruse' to 'Incruse plus Relvar'. The advertisements had remained on the media plan as 'Incruse' only. Following a broken link to the combined prescribing information, the media agency had requested replacement prescribing information for Incruse alone. Clause 4.2 listed the components of prescribing information which had to be provided according to the requirements of 4.1. Clause 4.4 described how the prescribing information as required by Clause 4.1 could be provided on digital material. It was not possible to breach either Clause 4.2 or 4.4; failure to provide the required information would be a breach of Clause 4.1. As the Relvar prescribing information had not been provided a breach of Clause 4.1 was ruled as acknowledged by GlaxoSmithKline. The Panel thus made no ruling in relation to Clauses 4.2 and 4.4.

The Panel noted that Clause 4.3 required the non-proprietary name of a medicine to appear immediately adjacent to the most prominent display of the brand name; for electronic advertisements the non-proprietary name had to be in a size such that it was readily readable. The Panel noted that although the advertisements at issue included the non-proprietary names in the correct position, the names were not readily readable. A breach of Clause 4.3 was ruled as acknowledged by GlaxoSmithKline.

The Panel noted that three of the advertisements at issue had been published online before final certification. A breach of Clause 14.1 was ruled as acknowledged by GlaxoSmithKline.

The Panel noted that Clause 28.1 of the Code required promotional material about prescription only medicines on the Internet and directed to a UK audience to comply with all of the relevant requirements of the Code. The Panel noted its rulings of breaches of the Code above and thus ruled a breach of Clause 28.1 as acknowledged by GlaxoSmithKline.

The Panel further noted that GlaxoSmithKline had admitted a breach of Clause 16.1 which required all relevant personnel concerned in anyway with the preparation or approval of material or activities

covered by the Code to be fully conversant with the Code and relevant laws and regulations. The Panel noted that although mistakes had been made it did not necessarily mean that personnel were not fully conversant with the Code; human error was always possible. No evidence had been provided to the Panel to demonstrate that relevant personnel had not been trained. On balance, the Panel ruled no breach of Clause 16.1.

Overall, the Panel considered that the failure to certify prior to publication, the omission of prescribing information for Relvar and the blurred non-proprietary names within the online advertisements meant that high standards had not been maintained. A breach of Clause 9.1 was ruled as acknowledged by GlaxoSmithKline.

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

Complaint received **7 August 2015**

Case completed **30 September 2015**

CASE AUTH/2791/9/15

ANONYMOUS, NON-CONTACTABLE v BAYER

Promotion of Xarelto

An anonymous, non-contactable complainant complained about the promotion of Xarelto (rivaroxaban) by Bayer plc. The material at issue was a leavepiece entitled 'Think NOACs [novel oral anticoagulants] and Renal Impairment in Non-Valvular AF [atrial fibrillation]. Think Xarelto'.

Xarelto was indicated for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (AF) with one or more risk factors, such as congestive heart failure (CHF), hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

The complainant drew attention to a table which compared Xarelto and two other NOACs; apixaban (Eliquis, Bristol-Myers Squibb) and dabigatran (Pradaxa, Boehringer Ingelheim), when there had been no head-to-head trials. The complainant stated that the footer tried to justify this but it was small and easily missed. In his/her view the data should not be displayed that way but if so, it should be very clear what each trial comprised.

The detailed response from Bayer is given below.

The Panel noted that no explanation was given and so in the Panel's view it was not immediately clear that the table presented the demography of the three studies and was not a comparison of safety or efficacy as submitted by Bayer. The Panel considered that the page was ambiguous as the comparative claim juxtaposed to the table 'Xarelto: Proven safety profile and efficacy in a higher-risk non-valvular AF patient population than any other NOAC' referenced to the three studies included within the table appeared to refer to the comparative data shown in the table. This was not so. Some readers might reasonably assume that there had been direct clinical comparisons of the safety profile and efficacy of Xarelto, Eliquis and Pradaxa which was not so. It appeared that the complainant might have been so misled. The footnote 'These trials were conducted with different designs and evaluated different populations, so direct comparisons of their results cannot be made' below the table was not sufficiently prominent or sufficiently clear to qualify the misleading impression. The footnote appeared to be inconsistent with Bayer's submission that the table presented demography not results. In addition, the Panel considered the page was such that on the balance of probabilities, some readers would assume that direct clinical comparisons of the three medicines' safety profile and efficacy in higher risk non-valvular AF-patient population had occurred which was not so.

The Panel considered that the table was misleading as alleged. Breaches of the Code were ruled.

An anonymous, non-contactable complainant complained about the promotion of Xarelto (rivaroxaban) by Bayer plc. The material at issue was a leavepiece (ref L.GB.12.2014.9153a) entitled 'Think NOACs [novel oral anticoagulants] and Renal Impairment in Non-Valvular AF [atrial fibrillation]. Think Xarelto'. The leavepiece stated that Xarelto was the only National Institute for Health and Clinical Excellence (NICE) approved NOAC with a prospectively tested renal dose (15mg once daily). The leavepiece was for the sales force to use with health professionals.

Xarelto was indicated for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (AF) with one or more risk factors, such as congestive heart failure (CHF), hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

COMPLAINT

The complainant drew attention to a table which compared three NOACs; rivaroxaban (Xarelto), apixaban (Eliquis, Bristol-Myers Squibb) and dabigatran (Pradaxa, Boehringer Ingelheim), when there had been no head-to-head trials. The footer tried to justify this but it was small and easily missed. The complainant did not consider that the data should be displayed that way but if so, it should also be very clear what each trial comprised.

When writing to Bayer, the Authority asked it to respond in relation to Clauses 7.2 and 7.3 of the Code.

RESPONSE

Bayer submitted that the presentation, format and content of the comparative table on page 5 were such that it did not mislead.

Bayer explained that ROCKET AF was a randomised double-blind, double dummy event-driven trial with an objective to demonstrate non-inferiority of rivaroxaban compared with warfarin in patients (n=14,264) with non-valvular atrial fibrillation who had a history of stroke or at least two additional independent risk factors for stroke. The primary efficacy endpoint was the composite of stroke and non-central nervous system (CNS) systemic embolism and the primary safety endpoint was the composite of major and clinically-relevant non-major bleeding. Patients were randomly assigned to receive either fixed dose rivaroxaban (20mg daily or 15mg daily in patients with a creatinine clearance of 30-49ml/min) or adjusted dose warfarin. Furthermore, with regard to renal impairment, the Xarelto summary of product characteristics (SPC) stated that:

'Limited clinical data for patients with severe renal impairment (creatinine clearance 15- 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min.

In patients with moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/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.'

With respect to the table at issue, Bayer stated that the CHADS2 scores (used to estimate stroke risk in patients with AF) for each anticoagulant were presented in three columns which were differentiated by colour and titles which specified the trial from which the data for each NOAC was derived. Furthermore, the trial title was in large upper case font. Bayer submitted that the differentiators for each column made it very clear that the data was derived from three different, separate trials and that there was nothing to suggest or imply that the trials were direct 'head-to-head' comparisons. This was reinforced by a footnote which emphasized that 'These trials were conducted with different designs and evaluated different populations so direct comparisons of their results cannot be made'.

Bayer submitted that the font size and contrast between the colour of the font and the background colour was such that it was not easily missed. The clarity of the footnote was such that its prominence was at least equivalent to that which was ordinarily seen in promotional and other materials designed for health professionals. Bayer noted that the table presented demography and was not a comparison of safety or efficacy.

Bayer stated that the table in question highlighted the mean CHADS2 score in all three relevant trials (ROCKET AF (Xarelto), ARISTOTLE (apixaban) and RE-LY (dabigatran)) and the percentage of patients in each sub-group that contributed to that score. The total number of patients in all three trials was also shown for comparison. The table therefore highlighted the higher risk non-valvular AF patient population according to the CHADS2 criteria in the ROCKET AF trial compared with ARISTOTLE and RE-LY.

Bayer noted that reference was also made to the fact that factors contributing to a higher risk of stroke might also contribute to renal impairment with the caveats of when and where Xarelto was licensed in this group of patients. The information was fully referenced in the material.

Bayer submitted that as per the SPC and clinical trial data the leavepiece made it clear that the Xarelto 15mg dose was intended for patients with non-valvular AF and for the appropriate severity of renal impairment.

Bayer therefore submitted that neither the table nor any of the accompanying information was misleading in breach of Clause 7.2. Furthermore, sufficient information was provided for the reader, so as not to mislead, however all three trials and the data shown were also clearly referenced if the reader wished to gain further information for each trial. Bayer also submitted that the principles of Clause 7.3 were maintained as the table compared medicines intended for the same purpose and no confusion was created between Bayer's or the competitor medicines.

PANEL RULING

The Panel noted 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 both parties. Complainants had the burden of proving their complaint on the balance of probabilities.

The Panel noted the allegation that the table in question was misleading as it compared three NOACs despite there being no head-to-head studies and the company's footnote could easily be missed due to its small font size.

The Panel noted that direct head-to-head studies were not necessarily needed to substantiate a comparison of products provided that such a comparison was not misleading and complied with the Code.

The Panel noted that page 5 of the leavepiece was headed 'Factors contributing to higher risk of stroke may also contribute to renal impairment'. Below the heading and directly above the table in question was the prominent claim 'Xarelto: Proven safety profile and efficacy in a higher risk non-valvular AF-patient population than any other NOAC'. The references to this claim included three studies; Patel et al, Granger et al and Connolly et al (Rocket AF, ARISTOTLE and RE-LY), which were compared in the table. The other three references cited related to ROCKET AF.

The Panel noted that the table in question featured the mean CHADS2 score and what appeared to be each of its five components (CHF, hypertension, ≥ 75 years old, diabetes and prior stroke or TIA) for all three trials (ROCKET AF (Xarelto), ARISTOTLE (apixaban) and RE-LY (dabigatran)). The percentage of patients in each component that contributed to that score was given. The figures for Xarelto were higher than the figures for apixaban and dabigatran.

The Panel noted Bayer's submission that the table was not a comparison of safety or efficacy and it highlighted the higher risk non-valvular AF patient population according to the CHADS2 criteria in the ROCKET AF trial compared with ARISTOTLE and RE-LY.

The Panel noted that no background information or explanation was given and so in the Panel's view it was not immediately clear that the table presented the demography of the three studies and was not a comparison of safety or efficacy as submitted

by Bayer. The Panel considered that the page was ambiguous as the comparative claim juxtaposed to the table 'Xarelto: Proven safety profile and efficacy in a higher-risk non-valvular AF patient population than any other NOAC' referenced to the three studies included within the table appeared to refer to, or be based on or substantiated by, the comparative data shown in the table. This was not so. Some readers might reasonably assume that there had been direct clinical comparisons of the safety profile and efficacy of Xarelto, Eliquis and Pradaxa which was not so. It appeared that the complainant might have been so misled. The Panel noted that the footnote 'These trials were conducted with different designs and evaluated different populations, so direct comparisons of their results cannot be made' which appeared in small typeface below the table was not sufficiently prominent or sufficiently clear to qualify the misleading impression of the page. The footnote appeared to be inconsistent with Bayer's submission that the table presented demography not results. In addition, the Panel considered the page was such that on the balance of probabilities, some readers would assume that direct clinical comparisons of the three medicines' safety profile and efficacy in higher risk non-valvular AF-patient population had occurred which was not so.

The Panel considered that the table was misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **3 September 2015**

Case completed **16 October 2015**

ANONYMOUS v GLAXOSMITHKLINE

SUMMIT study press release

An anonymous complainant, who was initially contactable but later could no longer be contacted at the email address provided and who described him/herself as a respiratory physician, alleged that a press release detailing results of the SUMMIT study issued by GlaxoSmithKline was deliberately misleading.

The SUMMIT [Study to Understand Mortality and Morbidity] in COPD [chronic obstructive pulmonary disease] study used, *inter alia*, Relvar (fluticasone 100mcg/vilanterol 25mcg) Ellipta. Relvar Ellipta's indications included the symptomatic treatment of adults with COPD with a FEV1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

The complainant was particularly concerned about a reference in the press release to 'survival' given that the study had failed to demonstrate a survival benefit for Relvar. The complainant was also concerned that the press release did not include a black triangle given that Relvar was subject to additional monitoring.

The complainant alleged that GlaxoSmithKline's attempt to disguise the failed results of the study could mislead clinicians. Further, by overtly promoting in the public press, such statements could raise unfounded hopes for patients. The complainant alleged that GlaxoSmithKline had brought disrepute to the whole industry.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that the SUMMIT baseline publication (Vestbo *et al,* 2012) described the study as a multicentre, randomised, double-blind, parallel group, placebo-controlled trial to investigate the impact of Relvar 100/25mcg and its components on the survival of patients with moderate COPD and either a history or increased risk of cardiovascular disease.

The Panel noted the complainant's allegation that referring in the press release to the study previously termed SUMMIT as a 'survival' study following release of the results which failed to demonstrate a survival benefit, along with the assertion that 'the risk of dying on [Relvar] 100/25mcg was 12.2% lower than on placebo', was an attempt to mislead health professionals, patients and the public.

The Panel noted that the press release was headed 'GSK and Theravance announce results from the SUMMIT COPD CV Survival Study'. Below the title and the issue date was the statement 'Issued: London, UK and South San Francisco, CA, USA – LSE [London Stock Exchange] announcement'. The first paragraph referred to the LSE, NYSE [New York Stock Exchange] and NASDAQ; the Panel considered that it was clear from the outset that the press release was aimed at financial markets; the intended audience was not clinicians, patients or the public. The first paragraph also briefly explained the study and the SUMMIT acronym but did not refer to survival. The second paragraph read 'For the primary endpoint of the study, the risk of dying on [Relvar] 100/25mcg was 12.2% lower than on placebo over the study period which was not statistically significant (p=0.137)'. The third paragraph referred to the results of the two secondary endpoint. Although one endpoint showed statistical significance in favour of Relvar, it stated that as the primary endpoint was not met, statistical significance could not be inferred from the result. The second secondary endpoint showed a trend in favour of Relvar which was not statistically significant.

The Panel noted that the study was referred to as the SUMMIT study in the title and throughout. The study was designed to investigate the impact of Relvar 100/25mcg and its components on risk of death/survival in selected COPD patients. In the Panel's view it was not unreasonable to refer to survival in the heading when describing the study provided that in doing so, readers would not be misled. In the Panel's view it was stated at the outset and throughout the press release that the study failed to meet its primary endpoint and the secondary endpoints were placed in the context of the failed primary outcome. The Panel did not consider that the title of the press release or description of the results implied a survival claim for Relvar. In that regard, the Panel noted that press articles appeared to show that the target audience had understood the results of the study. The Panel thus did not consider that the press release was misleading as alleged. No breaches of the Code were ruled.

The Panel noted the complainant's concern that the press release did not display a black triangle. The Panel considered that as the press release was not promotional, there was no requirement under the Code for it to include a black triangle. No breach of the Code was ruled.

The Panel noted GlaxoSmithKline's submission that the press release was specifically directed at shareholders and the financial community, not patients. The Panel noted that the press release contained information that might be of interest to patients but in the Panel's view it had not been directed at them. Furthermore, the results were presented in a balanced manner and the fact that the study failed to show a survival benefit was understood by the complainant, the financial journalists and it was therefore, in the Panel's

view, unlikely that the press release would raise unfounded hopes in patients who searched for it. The Panel ruled no breach of the Code. The Panel noted that the Code only required a statement about reporting side effects to be included on material which related to a medicine and was intended for patients taking that medicine. Although it might have been helpful to include information about reporting side effects, as the press release was not intended for patients the Panel ruled no breach of the Code.

The Panel noted its rulings above and considered that high standards had been maintained. No breach of the Code was ruled including no breach of Clause 2.

An anonymous complainant, who was initially contactable but later could no longer be contacted at the email address provided and who described him/herself as a respiratory physician, alleged that a press release entitled 'GSK and Theravance announce results from the SUMMIT [**S**tudy to **U**nderstand **M**ortality and **M**orbid**IT**y] COPD [chronic obstructive pulmonary disease] CV [cardiovascular] Survival Study' issued by GlaxoSmithKline was deliberately misleading. The complainant provided a link to the press release.

The study involved 16,485 COPD patients from 43 countries; each patient had moderate airflow limitation and either a history or increased risk of cardiovascular disease (CVD). Patients were randomly assigned to once daily treatment with GlaxoSmithKline's product Relvar Ellipta (100/25mcg fluticasone furoate/vilanterol (FF/VI)) FF (100mcg), VI (25mcg) or matched placebo. The primary endpoint of the study was the risk of dying on Relvar. Secondary endpoints were the rate of lung function decline and the risk of experiencing an on-treatment cardiovascular event (CV death, myocardial infarction, stroke, unstable angina and transient ischaemic attack).

Relvar Ellipta (100/25mcg) indications included the symptomatic treatment of adults with COPD with a FEV1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

COMPLAINT

The complainant submitted that in its attempt to fool the medical community and the public, GlaxoSmithKline labelled the latest failed fiasco study a COPD CV 'survival' study. The complainant alleged that use of the word survival was clearly intended to mislead the audience; the study had so far been referred to as the SUMMIT study however, at the release of the results, contrary to what the results showed, it had now been termed 'survival' study.

The complainant noted that the study clearly showed that Relvar failed to demonstrate a survival benefit compared with placebo. Nonetheless, use of the term 'survival' study along with GlaxoSmithKline's assertion that 'the risk of dying on [Relvar] 100/25mcg was 12.2% lower than on placebo' was a calculated attempt to mislead clinicians, patients and the public. In addition it was appalling that the press release failed to display a black triangle for Relvar, a legal requirement for the medicine which was subject to additional monitoring due to the several serious risks that it carried to patients including severe and fatal pneumonia.

The complainant stated that for years, GlaxoSmithKline promoted its medicine Seretide with the claim that it prolonged life in COPD, despite the failed TORCH trial and had been found in breach multiple times last year in relation to such promotion. However, it seemed that the lessons had not been learnt and the complainant alleged that GlaxoSmithKline continued to operate in a wilfully unethical manner both in the UK and abroad, referring to recent events in China and the previous findings by the US government. The complainant submitted that GlaxoSmithKline, as the largest pharmaceutical organisation in Britain, was morally obliged to lead by example, but it brought nothing other than disrepute to the whole industry.

The complainant alleged that GlaxoSmithKline's latest attempt to disguise the failed results of the study could mislead the clinicians. Further, by overtly promoting in the public press, such statements could raise unfounded hopes for patients.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 2, 4.11, 7.2, 7.4, 9.1, 26.2, and 26.3.

RESPONSE

GlaxoSmithKline submitted that it took compliance with the Code very seriously and denied that the press release was in breach of Clauses 2, 4.11, 7.2, 7.4, 9.1, 26.2 or 26.3.

GlaxoSmithKline noted that the complainant referred to a press release issued by GlaxoSmithKline Corporate Communications on 8 September 2015, in London and San Francisco, and which was placed in the 'Press Releases' section of the corporate website. It was also distributed to financial, medical and business institutions which had specifically asked to be informed of any new GlaxoSmithKline press releases.

GlaxoSmithKline stated that the press release was issued because the newsworthy study results were share price sensitive and of potential interest to shareholders and financial institutions. As such, before issuing the press release, the Stock Exchange listing for both companies (NYSE [New York Stock Exchange] and NASDAQ]) were informed of its release and were referred to in the first paragraph of the press release. The press release was also in line with the company's standard operating procedure on press releases which stated, 'We announce Phase III data via a corporate press release, regardless of outcome, upon first presentation or publication in a peer-review journal. Study results for material assets are disclosed via Stock Exchange Announcement when data analysis is complete'.

GlaxoSmithKline noted that the complainant had sourced the material from the press section of its website, either on the day it was released or shortly thereafter and had referred to it as a 'press release'.

Reference to 'survival' study

GlaxoSmithKline submitted that 'survival' was used once in the press release title, and only then as to describe the study design, as follows; 'GSK and Theravance announce results from the SUMMIT COPD CV Survival study'. The study was never simply referred to as a '... COPD CV "survival" study' as alleged. Furthermore the study was referred to as 'SUMMIT' six times; in the title in large and bold font, in the first paragraph to explain the acronym, by the senior vice president and head global respiratory franchise for GlaxoSmithKline, the study's principal investigator, and the chief executive officer for Theravance, as well as in the section which provided further information about the study itself.

GlaxoSmithKline noted that the study was officially listed on clinical trials.gov as:

> 'Study to Evaluate the Effect of Fluticasone Furuoate/Vilanterol on Survival in Subjects With Chronic Obstructive Pulmonary Disease' (emphasis added).

The rationale for the study in a baseline publication for the study design was given as:

> 'The "Study to Understand Mortality and Morbidity in COPD" (SUMMIT) aims at determining the impact of Fluticasone Furoate/ Vilanterol combination (FF/VI), and the individual components on the survival of patients with moderate COPD and either a history of CVD or at increased risk for CVD' (emphasis added).

The keywords to be used when searching for the study were: COPD; CVD; protocol; study design; mortality; survival; Fluticasone Furoate; Vilanterol; combination therapy (emphasis added).

GlaxoSmithKline explained that SUMMIT was an event-driven study designed to have 90% power to detect a 30% reduction in the risk of all-cause mortality. 'Survival' was frequently referred to in the baseline publication, eg 'Survival status of each subject will be recorded at every visit. For any subject who prematurely withdraws, survival status will be captured at 3-monthly intervals by means of telephone calls or other forms of contact' (emphasis added) (Vestbo *et al* 2012). Aside from that, 'survival' could be considered an acceptable descriptor for the study design, particularly as the financial community and shareholders, to whom the press release was directed, would probably not be familiar with the acronym, SUMMIT. Also where 'survival' was used in the title, there were no statements about the outcome of the study; it was used purely as an adjective for the study design, not as a claim.

GlaxoSmithKline therefore denied a breach of Clause 7.2 as well as Clause 7.4.

Alleged attempt to mislead the clinicians, patients and the public.

GlaxoSmithKline submitted that the complainant indicated that he/she had read the press release and understood its contents as he/she used such phrases as 'the study clearly showed' and 'failed to demonstrate a survival benefit'; the complainant thus demonstrated that even a 'critical reader' had understood that the study did not achieve its primary endpoint.

The fact that 'the primary endpoint was not statistically significant' was mentioned four times in the press release and that 'statistical significance could not be inferred from the secondary endpoints, as the primary endpoint was not met', twice. GlaxoSmithKline noted that the complainant's comment that the 'risk of dying on [Relvar] 100/25mcg was 12.2% lower than on placebo', failed to complete the sentence from the press release which continued '... over the trial period which was not statistically significant (p=0.137)'.

The complainant therefore clearly understood the results and significance for the SUMMIT study as did the audience for whom the release was intended, the global financial community, judging from the headlines and analyst reports which appeared worldwide on either the same, or following day after the announcement was made eg:

> 'Overnight GSK has reported that the SUMMIT COPD cardiovascular survival trial failed to meet its primary endpoint. SUMMIT compared [Relvar] to placebo in 16,485 patients with COPD and a history of or increased risk of cardiovascular disease. The aim was to show that treatment with [Relvar] improved cardiovascular survival. If successful, [Relvar] would have been the only COPD drug to have shown a survival benefit and the data would have provided a significant commercial boost to [Relvar] relative to competitors, especially in the face of generic Advair over time' Credit Suisse 9 September 2015.
>
> 'Respiratory drug trial failure deals blow to GSK revival plan' Financial Times and
>
> 'Study finds key GSK-Theravance Lung drug didn't extend lives' Washington Post.

GlaxoSmithKline therefore denied a breach of Clause 7.2 as well as Clause 7.4.

Failure to display a black triangle

GlaxoSmithKline submitted that the press release was targeted at shareholders and the financial community in line with Clause 26.2 'Information made available in order to inform shareholders, the Stock Exchange and the like by way of annual reports and announcements etc may relate to both existing medicines and those not yet marketed'. In addition, the press release was examined in line with the supplementary information to Clause 14.3 which stated 'Other material issued by companies which relates to medicines but which is not intended

as promotional material for those medicines per se, such as corporate advertising, press releases, market research material, financial information to inform ....' and signed as being fair, accurate, balanced and capable of substantiation by thirteen senior members of GlaxoSmithKline, including two statisticians.

As the press release was not a promotional item and was not specifically intended for prescribers or patients, it did not require a black triangle against the first/most prominent mention of the brand name, the significance of which would in any case not have been known to most of the financial community. This was in accordance with guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) about the yellow card scheme.

GlaxoSmithKline therefore denied a breach of Clause 4.11.

GlaxoSmithKline submitted the complainant's assumption that the 'additional monitoring (was) due to the several serious risks that [Relvar] carried to patients including severe and fatal pneumonia' was incorrect. GlaxoSmithKline stated that the black triangle was a requirement for all newly available medicines in the UK and could only be removed once the MHRA believed that the benefit:risk ratio of that medicine had been fully characterised. With regard to statements concerning 'severe and fatal pneumonia' GlaxoSmithKline noted that detailed safety information was given on pages 1 and 2 (relating to the study itself) and on pages 4-6 (relating to a more general overview of Relvar) of the press release.

Clauses 26.2 and 26.3

GlaxoSmithKline submitted that the press release gave an accurate, balanced view of a large important study, which failed to meet its primary endpoint, and within that context it provided information regarding the secondary endpoints. The press release was also balanced and fair in terms of the safety/tolerability information provided both with respect to the study and Relvar. The press release was specifically directed at shareholders and the financial community, not at patients who might have been prescribed Relvar.

GlaxoSmithKline therefore denied that the press release was in breach of Clause 26.2. GlaxoSmithKline did not consider that Clause 26.3 'Any material which relates to a medicine and which is intended for patients taking that medicine must include ...' was applicable as the press release was not specifically distributed to patients taking the medicine (or to potential prescribers); it was principally for the attention of shareholders and the financial community as well as the medical press.

In view of the above GlaxoSmithKline, therefore submitted that high standards had been maintained and that it had not brought the industry into disrepute as claimed; it denied breaches of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that Vestbo *et al* described the SUMMIT study as a multicentre, randomised, double-blind, parallel group, placebo-controlled trial to investigate the impact of Relvar 100/25mcg and its components on the survival of patients with moderate COPD and either a history or increased risk of cardiovascular disease.

The Panel noted the complainant's allegation that referring in the press release to the study previously termed SUMMIT as a 'survival' study following release of the results which failed to demonstrate a survival benefit, along with the assertion that 'the risk of dying on [Relvar] 100/25mcg was 12.2% lower than on placebo', was an attempt to mislead health professionals, patients and the public.

The Panel noted that the press release was dated 8 September 2015 and was headed 'GSK and Theravance announce results from the SUMMIT COPD CV Survival Study'. Below the title and the issue date was the statement 'Issued: London, UK and South San Francisco, CA, USA – LSE [London Stock Exchange] announcement'. The first paragraph referred to the LSE, NYSE and NASDAQ; the Panel considered that it was clear from the outset that the press release was aimed at financial markets; the intended audience was not clinicians, patients or the public as implied by the complainant. The first paragraph also briefly explained the study and the SUMMIT acronym but did not refer to survival. The second paragraph read 'For the primary endpoint of the study, the risk of dying on [Relvar] 100/25mcg was 12.2% lower than on placebo* over the study period which was not statistically significant (p=0.137)'. The asterisk was not explained. The third paragraph referred to the results of the two secondary endpoints; the rate of lung function decline which was reduced by 8ml/year in patients taking Relvar 100/25mcg compared with placebo (p=0.019). It stated that as the primary endpoint was not met, statistical significance could not be inferred from the result; and the risk of experiencing an on-treatment cardiovascular event (CV death, myocardial infarction, stroke, unstable angina and transient ischaemic attack) was 7.4% lower in patients taking Relvar 100/25mcg compared with placebo (p=0.475) which was noted as not being statistically significant.

The Panel noted GlaxoSmithKline's submission that 'survival' was used once in the press release title, and then only as a descriptor for the study design ie 'the SUMMIT COPD CV Survival Study' as opposed to 'a COPD CV survival study' as alleged. 'Survival' was otherwise only used three times more in the eight page press release. Furthermore, the study was referred to as 'SUMMIT' six times throughout the press release.

The Panel noted that the study was referred to as the SUMMIT study in the title and throughout. The study was designed to investigate the impact of Relvar 100/25mcg and its components on risk of death/survival in COPD patients with moderate airflow limitation and either a history or increased risk of cardiovascular disease. In the Panel's view it was

not unreasonable to refer to survival in the heading when describing the study provided that in doing so, readers would not be misled. In the Panel's view it was stated at the outset and throughout the press release that the study failed to meet its primary endpoint and the secondary endpoints were placed in the context of the failed primary outcome. The Panel did not consider that the title of the press release or description of the results implied a survival claim for Relvar. In that regard, the Panel noted that the articles quoted by GlaxoSmithKline appeared to show that the target audience had understood the results of the SUMMIT study as reported in the press release. The Panel thus did not consider that the press release was misleading as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted the complainant's concern that the press release did not display a black triangle. Clause 4.11 of the Code stated that when required by the licensing authority, all promotional material must show an inverted black triangle to denote that special reporting was required in relation to adverse reactions. The Panel considered that as the press release was not promotional, there was no requirement under the Code for it to include a black triangle. No breach of Clause 4.11 of the Code was ruled.

The Panel noted that Clause 26.2 stated 'Information about prescription only medicines which is made available to the public either directly or indirectly must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine'. The Panel noted GlaxoSmithKline's submission that the press release was specifically directed at shareholders and the financial community, not patients who might have been prescribed Relvar. The Panel noted that the press release contained information that might be of interest to patients but in the Panel's view it had not been directed at them. Furthermore, the results were presented in a balanced manner and the fact that the study failed to show a survival benefit was understood by the complainant, the financial journalists and it was therefore, in the Panel's view, unlikely that the press release would raise unfounded hopes in patients who searched for the press release on GlaxoSmithKline's website. The Panel ruled no breach of Clause 26.2. The Panel noted that Clause 26.3 only required a statement about reporting side effects to be included on material which related to a medicine and was intended for patients taking that medicine. Although it might have been helpful to include information about reporting side effects, as the press release was not intended for patients the Panel ruled no breach of Clause 26.3.

The Panel noted its rulings above and considered that 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 **25 September 2015**

Case completed **7 October 2015**

CASE AUTH/2794/9/15

BAYER v ACTAVIS

Promotion of Levosert

Bayer complained about a Levosert leavepiece issued by Actavis UK. Bayer marketed Mirena. Both Levosert and Mirena were intrauterine delivery systems (IUSs) each containing 52mg levonorgestrel; both were indicated as long acting, reversible contraceptives and of particular use in women with heavy menstrual bleeding who required contraception. Levosert was effective for 3 years and then should be removed; Mirena was effective for 5 years and then should be removed. Mirena was additionally indicated for protection from endometrial hyperplasia during oestrogen replacement therapy and was effective in that regard for 4 years after which it should be removed.

The detailed response from Actavis is given below.

Bayer alleged that the claim 'Can a single IUS be suitable for so many women?' was ambiguous, misleading, did not encourage the rational use of Levosert and could not be substantiated; it implied that Levosert was suitable for the majority of women/more women than other IUSs. Bayer noted that Levosert had a more limited licence than Mirena, with fewer indications and a shorter licensed duration of use, limiting its suitability for some women.

The Panel noted that although the title of the leavepiece 'Can a single IUS be suitable for so many women?' was presented as a question, the claim implied that Levosert was suitable for more women than other IUSs. In that regard, the Panel noted that Levosert was indicated for use in fewer women than Mirena as it was not indicated for protection from endometrial hyperplasia during oestrogen replacement therapy. As a contraceptive, Levosert was contraindicated in more women than Mirena as it could not be used in those with active or previous severe arterial disease such as stroke or myocardial infarction; such conditions were only contraindications for Mirena when it was used in conjunction with an oestrogen for hormone replacement therapy.

The Panel noted Actavis's reference to a 2005 review of Mirena which stated that the device was generally not recommended as the first method of choice in young, nulliparous women. Further, that the guidance had changed. In its updated clinical guideline on long-acting reversible contraception (LARC), the National Institute for Health and Care Excellence (NICE) now stated that all LARC methods were suitable for nulliparous women. Mirena was not contraindicated in nulliparous women. Overall the Panel considered that the claim implied that Levosert had a broader use than other IUSs which was not so. In the Panel's view the claim was misleading, could not be substantiated and did not encourage the rational use of Levosert. Breaches of the Code were ruled.

Bayer further alleged that the claim 'Levosert is available at a low acquisition cost. 25% saving compared to Mirena' was inaccurate and misleading. Levosert could not be compared with other IUSs and that the comparison with Mirena in particular could mislead by placing undue emphasis on the acquisition cost saving, without clearly stating that it had different licensed indications and duration of use. It was not a like-for-like comparison. For five years Mirena cost less per year than Levosert.

The Panel noted that the claim, on a page entitled 'Effective contraception for so many women', appeared in a prominent red circle on a white background. Above the circle was the statement 'All these benefits at a competitive price'. The Panel noted that the duration of effect of Levosert was shorter than that of Mirena and so in that regard their 'usage rates' differed. Levosert was effective for three years after which it had to be removed (a new IUS could be inserted if required); Mirena was effective for 5 years after which it had to be removed (again, a new IUS could be inserted if required). Levosert cost £66 (£22/year) and Mirena £88 (£17.60/year). The Panel noted that Actavis had submitted data to show that on average, women only retained Mirena for approximately 2 years and 10 months. From a population of 2,572, 53% of women retained Mirena for up to 3 years (ie for no longer than they could have retained Levosert). For these women it would have been less expensive if they had been prescribed Levosert. However, 47% of women used Mirena for longer than three years and for up to eight years. For women who used Mirena for no more than 8 years, it would have been less expensive to prescribe Mirena for the first five years and then switch to Levosert. The cost calculations were not straightforward.

The Panel considered that the claim at issue implied that the cost of contraception with Levosert would always be 25% less than with Mirena, which was not so. In the Panel's view the claim did not provide enough information for the prescriber to make a well informed decision. The Panel considered that the claim was misleading as alleged and a breach of the Code was ruled.

Bayer alleged that high standards had not been maintained.

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

Bayer complained about a four page Levosert leavepiece (ref UK/LE/0001/01-15b) issued by Actavis UK Ltd. Bayer marketed Mirena. Both Levosert and Mirena were intrauterine delivery systems (IUSs) each containing 52mg levonorgestrel; both were

indicated as long acting, reversible contraceptives (LARCs) and of particular use in women with heavy menstrual bleeding who required contraception. Levosert was effective for 3 years and then should be removed; Mirena was effective for 5 years and then should be removed. Mirena was additionally indicated for protection from endometrial hyperplasia during oestrogen replacement therapy and was effective in that regard for 4 years after which it should be removed.

1 Claim 'Can a single IUS be suitable for so many women?'

This claim appeared as the title on the outside cover of the leavepiece.

COMPLAINT

Bayer alleged that the claim was ambiguous and misleading. Although it was posed as a stylised question, it was an implied claim which indicated that 'a single IUS' ie Levosert was suitable for the majority of women/more women than other IUS options. Bayer noted that Levosert had a more limited licence than Mirena, with fewer indications and a shorter licensed duration of use, limiting its suitability for some women. Bayer alleged that the ambiguous statement did not encourage the rational use of Levosert, it was all-embracing and could not be substantiated. Bayer alleged breaches of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Actavis submitted that Bayer's comparison with Mirena was irrelevant as the title was not a comparison and Clause 7.3 had not been cited.

Actavis agreed that the title 'Can a single IUS be suitable for so many women?' was a question and one that challenged health professionals who delivered contraceptive services to consider the suitability of a new product, Levosert, to many different types of women. This had been carefully reinforced by the imagery, which sensibly did not portray every type of woman, nor fill the page with lots of women.

Actavis submitted that in its view it had not stated or implied that all women or the majority of them should be prescribed Levosert. The title was a claim and was placed as a question to encourage further thought on this matter and encourage prescribers to consider the suitability of Levosert as a new IUS, for women they might not have originally considered (such as young nulliparous women). Importantly, the claim was in line with the recommendation from the National Institute for Health and Care Excellence (NICE) that an increase in the uptake LARCs would reduce the number of unintended pregnancies.

In terms of substantiation for the claim, Actavis noted that Levosert was studied in a very large IUS study, which included many diverse groups of women including a high percentage of nulliparous women, parous women, women aged between 16–45 years, and with a range of body mass indices (Eisenberg *et al* 2015).

Actavis also noted that an old review article on Mirena stated that its use 'was not generally recommended as the first method of choice for young nulliparous women' (Sitruk-Ware and Inki 2005). Guidance had changed over the years and the young, nulliparous women in the Levosert study were especially important to consider in light of the recommendation from NICE about the uptake of LARCs.

Actavis therefore submitted that the claim 'Can a single IUS be suitable for so many women?' was not misleading, all-embracing or incapable of substantiation and therefore it denied any breach of Clauses 7.2, 7.4 or 7.10.

PANEL RULING

The Panel noted that the title of the leavepiece was 'Can a single IUS be suitable for so many women?'. Above the claim was the stylised drawing of what seemed to be three different head shots of the same young woman. The Panel noted that although the claim was presented as a question, it implied that Levosert was suitable for more women than other IUSs. The Panel noted Actavis's submission that the question prompted health professionals to consider using Levosert. In that regard, the Panel noted that Levosert was indicated for use in fewer women than Mirena in than Levosert was not indicated for protection from endometrial hyperplasia during oestrogen replacement therapy. In terms of its use as a contraceptive, Levosert was contraindicated in more women than Mirena in that it could not be used in those with active or previous severe arterial disease such as stroke or myocardial infarction. Active or previous severe arterial disease, such as stroke or myocardial infarction was only a contraindication when Mirena was used in conjunction with an oestrogen for hormone replacement therapy.

The Panel noted Actavis's reference to a 2005 review of Mirena which stated that the device was generally not recommended as the first method of choice in young, nulliparous women. Further, that the guidance had changed. In its updated clinical guideline on LARC, NICE now stated that all LARC methods were suitable for nulliparous women. Mirena was not contraindicated in nulliparous women.

Overall the Panel considered that the claim implied that Levosert had a broader use than other IUSs which was not so. In the Panel's view the claim was misleading and a breach of Clause 7.2 was ruled. The Panel further considered that the implied claim could not be substantiated and a breach of Clause 7.4 was ruled. The Panel considered that the claim did not encourage the rational use of Levosert. A breach of Clause 7.10 was ruled.

2 Claim 'Levosert is available at a low acquisition cost. 25% saving compared to Mirena'

This claim appeared on page 3 of the leavepiece.

COMPLAINT

Bayer noted that whilst Actavis had agreed to make the licensed duration of use more prominent in its materials, it refuted the need to make it clear that Levosert had a shorter licensed duration when it made claims about cost.

Bayer noted that page three of the leavepiece stated 'All these benefits at a competitive price' and 'Levosert is available at a low acquisition cost. 25% saving compared to Mirena'. Bayer alleged a breach of Clause 7.2 as the supplementary information stated 'Price comparisons, as with any comparison, must be accurate, fair and must not mislead. Valid comparisons can only be made where like is compared with like'. Bayer alleged that Levosert could not be compared with other IUSs and that this comparison with Mirena in particular could mislead by placing undue emphasis on the acquisition cost saving, without clearly stating that it had different licensed indications and duration of use. It was not a like-for-like comparison. The acquisition cost of Mirena was £88 while Levosert cost £66. If used in line with licensed durations of five and three years respectively, Mirena cost £17.60 per year, whereas Levosert cost of £22 per year. For five years Mirena cost less per year than Levosert. Bayer alleged that the claim was thus inaccurate and misleading to prescribers.

RESPONSE

Actavis stated that the claim was clear both in intent and impression; it referred to the 'acquisition cost' alone and did not incorrectly imply costs per year or cost-effectiveness.

Actavis stated that it had taken various PMCPA rulings into account when it created and approved the use of the claim, notably Cases AUTH/2638/9/13 and AUTH/2639/9/13, where the Panel commented that 'comparisons based on acquisition cost alone were not prohibited by the Code'.

Actavis stated that although Bayer asserted that 'Levosert could not be compared with other IUSs', it considered that it was valid to compare costs of Levosert with Mirena as long as this was made on the basis of the equivalent dosage requirement for the same indications. Levosert and Mirena were both IUSs that contained the same total amount of levonorgestrel with a similar release profile and both were licensed for contraception. Further, the claim was on a page entitled 'Effective contraception for so many women'. Therefore it was clear that contraception was the indication being discussed.

Actavis noted Bayer's view that if Levosert and Mirena were 'used in line with licensed durations …' then their respective costs per year differed. This would be true if there was evidence to suggest that all Mirena patients retained their IUS for 5 years. A retrospective analysis of anonymised electronic patient records for patients who had been prescribed Mirena (in 2006/7 and followed longitudinally until 2013), suggested the mean average duration of insertion was 2.82 years; only 1/3 abided to the 5 year licence (34.8%).

Actavis also noted that NICE reported that up to 60% of women stopped using their IUS within 5 years for various reasons. This was not an insignificant number and therefore it was entirely appropriate to compare Levosert and Mirena acquisition costs, so that a health professional could make informed decisions, particularly if they had previous experience of patients retaining their IUS for up to 3 years. The claim was clear in that acquisition costs alone were compared and not costs/year.

Therefore Actavis submitted that the claim 'Levosert is available at a low acquisition cost, 25% saving compared with Mirena' was accurate, not misleading and it denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that comparisons based on acquisition cost alone were not prohibited by the Code. The supplementary information to Clause 7.2 made it clear that, as with any comparison, price comparisons must be accurate, fair and must not mislead. Valid comparisons could only be made where like was compared with like. It followed therefore that a price comparison should be made on the basis of the equivalent dosage requirement for the same indications. For example to compare the cost per ml for topical preparations was likely to mislead unless it could be shown that their usage rates were similar or, where this was not possible, for the comparison to be qualified in such a way as to indicate that usage rates differed.

The Panel noted that the claim at issue, 'Levosert is available at a low acquisition cost. 25% saving compared to Mirena' appeared in a prominent red circle on a white background. Above the circle was the statement 'All these benefits at a competitive price'. The Panel noted that the duration of effect of Levosert was shorter than that of Mirena and so in that regard their 'usage rates' differed. Levosert was effective for three years after which it had to be removed (a new IUS could be inserted if required); Mirena, with which it was compared, was effective for 5 years after which it had to be removed (again, a new IUS could be inserted if required). The cost of Levosert was £66 (£22/year) and the cost of Mirena was £88 (£17.60/year). The Panel noted that Actavis submitted data to show that on average, women only retained Mirena for approximately 2 years and 10 months. From a population of 2,572, 53% of women (n=1,372) retained Mirena for up to 3 years (ie for no longer than they could have retained Levosert). For these women it would have been less expensive if they had been prescribed Levosert. However, 47% of women (n=1,200) retained Mirena for longer than three years and used it for up to eight years. For women who used Mirena for no more than 8 years, it would have been less expensive to prescribe Mirena for the first five years and then switch to Levosert. The cost calculations were not straightforward.

The Panel considered that the claim at issue implied that the cost of contraception with Levosert would always be 25% less than with Mirena, which was not so. In the Panel's view the claim did not provide

enough information for the prescriber to make a well informed decision. The Panel considered that the claim was misleading as alleged and a breach of Clause 7.2 was ruled.

3 Alleged breach of Clause 9.1

COMPLAINT

Bayer alleged that in persisting with the claims referred to above which misled prescribers and other decision makers, Actavis had failed to maintain high standards in breach of Clause 9.1.

RESPONSE

Actavis submitted that compliance with the Code was taken very seriously across the organisation. Clear reasons had been given as to why the Code had not been breached in relation to Bayer's allegations above. It therefore followed that high standards had been maintained and there was no breach of Clause of 9.1.

PANEL RULING

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

Complaint received **11 September 2015**

Case completed **21 October 2015**

CODE OF PRACTICE REVIEW – November 2015

Cases in which a breach of the Code was ruled are indexed in **bold type.**

AUTH/2754/5/15	**Anonymous, non-contactable nurse v Merck Serono**	**Call frequency**	**Breaches Clauses 15.2 and 15.4**	**No appeal**	**Page 3**
AUTH/2755/5/15	**Head of medicines optimisation v A Menarini**	**Promotion of Adenuric**	**Breaches of Clauses 7.2, 7.8, 9.1, 9.9 and 11.3**	**No appeal**	**Page 8**
AUTH/2756/5/15	**Anonymous employee v Merck Serono**	**Call rates**	**Breaches Clauses 15.2, 15.4 and 15.9**	**No appeal**	**Page 12**
AUTH/2758/5/15	**Galen v Stirling Anglian**	**Promotion of CosmoCol**	**Breaches Clauses 4.3, 5.2 and 5.4**	**No appeal**	**Page 18**
AUTH/2774/6/15	Head of medicines management v Pfizer	Gabapentin Patient Alert	No Breach	No appeal	Page 21
AUTH/2775/6/15	Anonymous, non-contactable pharmacist v Boehringer Ingelheim	Ofev supply programme	No Breach	No appeal	Page 27
AUTH/2776/7/15	Bristol-Myers Squibb and Pfizer/ Director v Bayer	Alleged breach of undertaking	No Breach	No appeal	Page 31
AUTH/2777/7/15	Anonymous, non-contactable v Sanofi	Representatives' business cards	No Breach	No appeal	Page 35
AUTH/2778/7/15	**Merz v Ipsen**	**Promotion of Dysport**	**Two breaches Clause 7.2 Two breaches Clause 7.3 Breaches Clauses 7.4 and 7.10**	**No appeal**	**Page 36**
AUTH/2779/7/15	General Practitioner v Merck Sharp & Dohme	Conduct of a representative	No breach	No appeal	Page 44
AUTH/2781/3/15	AbbVie v Bristol-Myers Squibb	Alleged off-licence promotion disguised as a medical symposium	No breach	No appeal	Page 46
AUTH/2782/7/15	**Voluntary admission by GlaxoSmithKline**	**Patient support items distributed from exhibition stand**	**Breaches Clauses 9.1 and 18.2**	**No appeal**	**Page 55**
AUTH/2784/7/15	Anonymous, non-contactable ex-employee v Chiesi	Alleged failure to certify materials	No breach	No appeal	Page 58
AUTH/2785/8/15	**Anonymous, non-contactable consultant v Bayer**	**Promotion of Eylea**	**Breaches Clauses 7.2, 7.3, 9.1, 15.2 and 15.9**	**No appeal**	**Page 60**
AUTH/2786/8/15	Primary care pharmacist v UCB	Keppra information on a nurses' website	No breach	No appeal	Page 67
AUTH/2787/8/15	**Voluntary admission by GlaxoSmithKline**	**Online advertisements for Incruse and Relvar**	**Breaches Clauses 4.1, 4.3, 9.1, 14.1 and 28.1**	**No appeal**	**Page 69**

AUTH/2791/9/15	**Anonymous, non-contactable v Bayer**	**Promotion of Xarelto**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 74**
AUTH/2792/9/15	Anonymous v GlaxoSmithKline	SUMMIT study press release	No breach	No appeal	Page 77
AUTH/2794/9/15	**Bayer v Actavis**	**Promotion of Levosert**	**Two breaches Clause 7.2 Breaches Clauses 7.4, 7.10 and 9.1**	**No appeal**	**Page 82**

PMCPA | Prescription Medicines Code of Practice Authority

The Prescription Medicines Code of Practice Authority was established by the Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself. Compliance with the Code is obligatory for ABPI member companies and, in addition, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and other relevant decision makers and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including any printed or electronic material used by them
- the supply of samples
- the provision of inducements in connection with the promotion of medicines and inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems, social media and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- disclosure of tranfers of value to health professionals and organisations
- joint working between the NHS and pharmaceutical companies
- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants, donations and benefits in kind to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of three of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member does not participate and is not present when the Panel considers it.

Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, must be in a majority when matters are considered by the Appeal Board.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Further information about the Authority and the Code can be found at www.pmcpa.org.uk

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria St, London SW1E 6QT

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