NUMBER 76 May 2012

CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

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

AMENDMENTS TO THE ABPI CODE OF PRACTICE FOR THE PHARMACEUTICAL INDUSTRY 2012

Proposals to amend the ABPI Code of Practice for the Pharmaceutical Industry were agreed by the ABPI on 11 June 2012.

The amendments result from changes to the Code of Practice of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and to UK law.

As a member of IFPMA, the Association of the British Pharmaceutical Industry (ABPI) is obliged to bring its Code into line with that of IFPMA. UK law relating to medicines is currently being amended and consolidated in The Human Medicines Regulations 2012. The new regulations are expected to be published in June and made law in early July.

Provided there are no changes required following publication of the new regulations, the Second 2012 Edition of the Code will come into operation on 1 July 2012 but with a transitional period before becoming fully operative on 1 November 2012. The updated Code of Practice will be available on the PMCPA website.

2011 ANNUAL REPORT

The 2011 Annual Report for the PMCPA will be available shortly.

PUBLIC REPRIMAND FOR GRÜNENTHAL

Grünenthal has been publicly reprimanded by the Code of Practice Appeal Board for providing misinformation in its response to recommendations following an audit required by the Appeal Board (Case AUTH/2327/6/10).

In 2010 the Code of Practice Panel ruled breaches of the Code in relation to the activities of Grünenthal's health economic liaison managers which amounted to the promotion of its then unlicensed medicine, tapentadol.

The Panel reported Grünenthal to the Appeal Board. On consideration of that report in September 2010, the Appeal Board was very concerned about Grünenthal's conduct. The prohibition on the promotion of a medicine prior to the receipt of its marketing authorization should have been well understood. The Appeal Board queried whether the senior management team had exercised sufficient control over the market access team. The Appeal Board required an audit of Grünenthal's procedures in relation to the Code and subsequent re-audits.

Upon consideration of the third audit report in November 2011 the Appeal Board was extremely concerned to note errors in Grünenthal's response to the recommendations from the second audit. This was unacceptable. The failure of senior employees to respond in full led the Appeal Board to question the company's commitment to compliance.

Upon consideration of the fourth and final audit report in March 2012 the Appeal Board noted significant changes within Grünenthal and encouraging progress since the previous audit. On the basis that the company adopted an approach of continual improvement the Appeal Board considered that no further action was required.

Full details of Case AUTH/2327/6/10 can be found on page 3 of this issue of the Review.

REPRESENTATIVES PAYING FOR INTERVIEWS

The Authority is sometimes advised that healthcare organizations or private service providers have requested that representatives pay for appointments with health professionals. When sufficient information is available the Authority will write to the organization or provider concerned to highlight the requirements of the Code. These include Clause 15.3 that: 'Representatives must not employ any inducement or subterfuge to gain an interview. No fee should be paid or offered for the grant of an interview.' and the supplementary information, Donations to Charities, which states that donations to charities in return for representatives gaining interviews are prohibited. Further supplementary information to the same clause, headed Health Professionals' Codes of Conduct, states that the GMC advises doctors that 'You must act in your patients' best interests when making referrals and when providing or arranging treatment or care. You must not ask for or accept any inducement, gift or hospitality which may affect or be seen to affect the way you prescribe for, treat or refer patients'. Similar provisions are in the professional codes for pharmacists and nurses.

Companies receiving requests for inappropriate payments are invited to forward relevant documentation to the Authority. The identity of the pharmaceutical company providing such information to the Authority is not revealed to the organization or provider.

CODE OF PRACTICE TRAINING

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

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

The next Code of Practice seminar date on which places remain available is:
Monday, 24 September

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

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

HOW TO CONTACT THE AUTHORITY

Our address is:
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Telephone:	020 7747 8880
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Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or email matthews@pmcpa.org.uk).

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

Heather Simmonds:	020 7747 1438
Etta Logan:	020 7747 1405
Jane Landles:	020 7747 1415
Ros Henley:	020 7747 8883

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

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

CASE AUTH/2327/6/10

MHRA v GRÜNENTHAL

Promotion of tapentadol

The Medicines and Healthcare products Regulatory Agency (MHRA) advised the Authority that it was concerned that Grünenthal was promoting its unlicensed medicine, tapentadol, to health professionals. The matter was taken up as a complaint under the Code.

The MHRA explained that it had received an allegation that suggested that Grünenthal had promoted its unlicensed product, tapentadol, to health professionals. The MHRA knew from previous correspondence with the company that its team of health economic liaison managers (HELMs) contacted 3,000 health professionals about the product's budgetary implications in advance of the grant of a marketing authorization. The MHRA deemed this activity to be promotional and provided advice on compliance with the law. A report of the case was provided.

The anonymous source alleged that the company had continued to target health professionals and it set call rates for this and had supporting materials, including slides, to use in proactive discussions with NHS staff.

The MHRA would take a very serious view of any further promotion of tapentadol in advance of the grant of a marketing authorization since Grünenthal had already been censured by the MHRA for the previous case. In addition the MHRA had asked to vet all promotional and related materials for the product, including any proactive materials for use by HELMs.

In the absence of any evidence of actual promotion from a recipient, the MHRA did not consider it appropriate to take forward a legal investigation for breach of the regulations. Instead it asked the Authority to investigate Grünenthal's actions to ensure that it had not promoted tapentadol and that it had appropriate procedures and controls in place for its HELMs and any other staff that might discuss unlicensed medicines with health professionals.

The detailed response from Grünenthal is given below.

The Panel noted that the complaint from an anonymous source to the MHRA was that Grünenthal continued to promote tapentadol prior to the grant of a marketing authorization. The MHRA had received a complaint about the matter in November 2009 and had agreed action with Grünenthal in January 2010. The Panel noted that the MHRA had considered the activities in relation to the Advertising Regulations and the Blue Guide. The Panel considered that it was limited to considering Grünenthal's activities after January 2010 in relation to the Code.

The Panel noted Grünenthal's comments about the anonymous source of the complaint to the MHRA and the burden of proof. The Panel noted, as set out in the introduction to the Constitution and Procedure, that complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties.

The Panel noted that Grünenthal had begun an advance notification process for tapentadol in November 2009 ie only 10 months before it anticipated having a marketing authorization for the medicine. In that regard, the Panel queried whether the information had been supplied early enough such that budget holders etc could be reasonably expected to act upon it. Information could only be supplied if the product had a significant budgetary implication. The Panel queried whether this was so but did not consider this was relevant to the complaint before it.

It appeared, that, in compliance with a request from the MHRA, that whilst HELMs were not given any printed material regarding tapentadol, they could still talk about it. The Panel considered that this approach was wholly unacceptable. The HELMS were given, inter alia, information about tapentadol some of which was headed 'not approved for distribution'. Some of this material showed an advantage for tapentadol vs oxycodone. In the Panel's view, the more information the HELMs were given about tapentadol the more likely they were to use it with their customers for commercial advantage.

The Panel noted Grünenthal's submission that the HELMs had not engaged in any proactive advance notification for tapentadol following an agreement with the MHRA in January. It appeared that since then the HELMs had undertaken a formulary mapping exercise to gain an understanding of how a new medicine would be introduced into the local health economy. This exercise required the HELMs to seek answers to a number of key business questions. Some of those questions were detailed in a briefing presentation, 2 March, and included the following: 'Identify attitudes to [controlled drugs] and tapentadol in nociceptive neuropathic and specifically back pain'; 'Where do they see tapentadol on the analgesic ladder?'; 'Where does the customer see a new pain drug adding most value?' and 'Does [drug and therapeutics] need to be achieved before a new pain drug can be used?'. The Panel noted Grünenthal's submission that following dialogue with the MHRA in April 2010, HELMs were briefed to discuss the process issues in relation to new products in general. Further formulary mapping questions appeared in a presentation dated 28 April 2010.

The Panel noted that the HELMs visited individuals responsible for the approval and purchase of medicines within the NHS; they also visited those who had to gain approval for the use of medicines in local health economies. The HELMs proactively saw both types of customers in relation to Grünenthal's licensed products all of which were for pain relief. The Panel considered that in this regard customers would see the HELMs as medical representatives. To have that same group of people then asking questions about tapentadol or a 'new pain drug' would be seen as promotional.

The Panel disagreed with Grünenthal's submission that the HELM position was a non-promotional role. Their activities were not limited to a fact finding role as the nature of the questions they were to ask would raise interest and awareness in the new product and solicit questions about it. The slides presented to the HELMs about tapentadol reinforced the promotional aspect of their activity. The HELMs were expected to have selling skills and they visited the same people to tell them about licensed medicines and to ask them questions about tapentadol and/or 'a new pain drug'. In the Panel's view asking such questions amounted to the promotion of tapentadol before the grant of its marketing authorization. Thus a breach of the Code was ruled. The Panel considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel considered that to brief a team, employed for its selling skills, to raise the profile of tapentadol and/or 'a new pain drug' just weeks before the expected grant of a marketing authorization was unacceptable. The Panel was very concerned about the failure to provide the HELMs with clear written instruction and this was a particularly serious omission given the concerns raised by the MHRA about the activity. The Panel considered that the activity amounted to a softening of the market. Such activity brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of the Code was ruled.

The Panel was extremely concerned about Grünenthal's activities with regard to the advanced notification of tapentadol. The MHRA had provided advice to the company following a mailing about tapentadol to 3,000 people. Since being in correspondence with the MHRA, Grünenthal had used a team of HELMs to gather information about, inter alia, attitudes to tapentadol and how to get 'a new pain drug' on to a formulary. The HELMs were expected to have selling skills and saw some of the same people about licensed and unlicensed medicines. The HELMs were expected to work closely with the sales team. Briefings to HELMs about this matter after the intervention of the MHRA were inadequate. Overall the Panel considered that Grünenthal's activity amounted to the promotion of tapentadol prior to the grant of its licence. In the Panel's view the HELMs' activities did not constitute the advance notification of tapentadol as no information was being supplied that showed that the product would have a significant budgetary effect. The Panel considered that overall Grünenthal's actions were unacceptable. The Panel decided to report the company to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. The Panel noted Grünenthal's submission that on receipt of this complaint it had suspended all formulary mapping activities.

The Appeal Board noted from the company representatives that Grünenthal had originally set up a market access team to try to limit the extensive off-label use of Versatis and to gain market access for its portfolio of licensed pain medicines. Part of the HELMs' role was to promote Grünenthal's medicines. The company had then used this same team, with the same job description, to work on the advance notification of tapentadol. The Appeal Board was very concerned about the conduct of Grünenthal. The prohibition on the promotion of a medicine prior to the receipt of its marketing authorization should have been well understood. It appeared that Grünenthal had not taken the opportunity to thoroughly review the HELMs' role and responsibilities when the MHRA had determined that, in providing advance notification, they had infact promoted tapentadol prior to the grant of its marketing authorization. Although changes had been made to the way the HELMs worked at this point, in that they had no role in relation to advance notification, the account mapping and other activities which they carried out were considered by the Panel to still amount to the promotion of a medicine prior to the grant of its marketing authorization. This was unacceptable.

The Appeal Board was very concerned to learn that the market access team had generated presentations and briefing materials for the HELMs which had not been certified. In that regard the Appeal Board queried whether the senior management team had exercised sufficient control over the market access team especially considering it was newly appointed, had responsibilities for an unlicensed medicine and the MHRA's involvement in the matter.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of Grünenthal's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the audit report (October 2010) the Appeal Board noted that Grünenthal had agreed compliance plans which would address all the areas recommended for attention and this was already being implemented.

The Appeal Board decided that a second audit should be carried out in February 2011 when it would expect the recommendations in the audit report to be implemented. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the second audit report (delayed until March 2011) the Appeal Board was encouraged by Grünenthal's progress since October but considered that the company still needed to demonstrate that it understood the importance of compliance. The Code and its requirements needed to become embedded into all levels of the company.

The Appeal Board decided that a third audit should be carried out in September when it would expect the recommendations in the audit report to be implemented. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon consideration of the third audit the Appeal Board was concerned that it still appeared that the company had not really understood the seriousness of the situation. The Appeal Board was extremely concerned to note errors in the response from Grünenthal to the recommendations from the March 2011 audit (part of the preparation for the September 2011 audit). This was unacceptable. It was hard to believe, given the recommendation in March that the company should be confident that all the Versatis material was clear regarding the licensed indication, that the company had not been precise about what had been done. Senior employees had not taken decisive action to implement the recommendation. The failure of senior employees to respond in full to questions at the audit about that recommendation led the Appeal Board to question the company's stated commitment to compliance.

The Appeal Board decided that Grünenthal should be publicly reprimanded in relation to the misinformation in its response to the Authority. Prior to the third audit the Appeal Board was extremely concerned about the apparent lack of demonstrated change in the company culture. It noted that some activities had been started and these might improve the situation. A new general manager was appointed in October. The Appeal Board decided that a fourth audit of Grünenthal should take place by mid February 2012. Upon receipt of the report for that audit, it would decide whether further action was needed.

Upon consideration of the forth audit report (February 2012) the Appeal Board noted that Grünenthal had undergone changes in senior staff including a new general manager. There appeared to be a different culture in the company and a more positive attitude to compliance. The Appeal Board considered that there had been encouraging progress since the last audit. On the basis that the company adopted an approach of continual improvement the Appeal Board considered that no further action was required.

The Medicines and Healthcare products Regulatory Agency (MHRA) advised the Authority that it was concerned that Grünenthal was promoting its unlicensed medicine, tapentadol, to health professionals. The matter was taken up as a complaint under the Code.

Tapentadol had a combined mechanism of action, mu-opioid-receptor agonism (MOR) and noradrenaline reuptake inhibition (NRI).

COMPLAINT

The MHRA explained that it had received an allegation that suggested that Grünenthal had promoted its unlicensed product, tapentadol, to health professionals. The MHRA knew from previous correspondence with the company that its team of health economic liaison managers (HELMs) contacted 3,000 health professionals about the product's budgetary implications in advance of the grant of a marketing authorization. The MHRA deemed this activity to be promotional and provided advice on compliance with the law. A report of the case was provided.

The anonymous source alleged that the company had continued to target health professionals and it set call rates for this and had supporting materials, including slides, to use in proactive discussions with NHS staff.

The MHRA would take a very serious view of any further promotion of tapentadol in advance of the grant of a marketing authorization since Grünenthal had already been censured by the MHRA for the previous case. In addition the MHRA had asked to vet all promotional and related materials for the product, including any proactive materials for use by HELMs.

In the absence of any evidence of actual promotion from a recipient, the MHRA did not consider it appropriate to take forward a legal investigation for breach of the regulations. Rather the MHRA asked the Authority to investigate Grünenthal's actions to ensure that it had not promoted tapentadol and that it had appropriate procedures and controls in place for its HELMs and any other staff that might discuss unlicensed medicines with health professionals.

When writing to Grünenthal, the Authority asked it to respond in relation to Clauses 2, 3.1 and 9.1 of the Code.

RESPONSE

Grünenthal submitted that it took this matter very seriously and was undertaking a thorough investigation into the anonymous, unsubstantiated allegation forwarded from the MHRA that 'the company had continued to target health professionals and it set call rates for this and had supporting materials, including slide sets, to use in proactive discussions with NHS staff'. Grünenthal concluded that the allegation was without merit.

Grünenthal noted that the Code allowed for advanced notification of products (in accordance with Clause 3.1) so that NHS budget holders and those with policy influence could forward plan for products to be introduced where such products might have a significant budgetary impact.

Grünenthal anticipated that tapentadol (trade name Palexia) would receive UK marketing authorization in September 2010 and that it would have a significant budgetary impact on the NHS. The reasons for the significant budgetary impact were as set out in a document compiled in discussion with the MHRA but never used. A copy of the document was provided. As NHS budget holders and policy makers might often need a considerable lead time to plan, Grünenthal began an advance notification process, including a certified letter sent in November 2009, the intention being to send that letter to a small number of such budget holders/policy makers. The letter to identified budget holders/policy makers set out a limited set of facts about tapentadol (which in Grünenthal's view was in line with Clause 3.1 supplementary information) and offered a HELM to visit to discuss the details of the budgetary impact.

Grünenthal submitted that a complaint (anonymised to Grünenthal) was received by the MHRA in November 2009. The MHRA contacted Grünenthal on 26 November concerned that the advance notification letter that Grünenthal had sent out did not comply with Section 4.2 of the MHRA's Blue Guide and that the HELM visit being offered was promotional in nature. Grünenthal wrote to the MHRA on 1 December to confirm that further dissemination of this letter and similar materials, as well as meetings, had been suspended pending resolution of the case.

Grünenthal discovered that the letter had been sent by one of its employees to approximately 3,000 people, some of whom had responsibilities that were not primarily related to budgets or policy making. Grünenthal took this matter very seriously, admitted the error and apologised to the MHRA. Grünenthal agreed to make no further use of the letter and to implement processes to check all future distribution lists of mailings. That matter concluded with a summary report published by the MHRA on 11 March 2010. Grünenthal considered the matter closed and had had no further contact with the MHRA on this matter.

With the continuing desire to fully comply with all applicable rules Grünenthal sought clarification from the MHRA about exactly what materials the MHRA needed in respect of advance notification in order to review how it could proceed with this business process. Grünenthal put forward proposals on how it might go about the advance notification process and how it might confirm the exact identity and ascertain the specific interest of named budget holders/policy makers and offer a meeting with a HELM. Two draft briefing documents were rejected by the MHRA and therefore had never been used (copies were provided).

More generally, Grünenthal submitted that it had a number of processes in place to address the MHRA's concerns and to comply with the rules:

- Medical information routinely handled tapentadol enquiries; all enquiries went to medical information for review. Only on a specific request would tapentadol information be given out by medical information, and all such requests were recorded and tracked in a medical tracking system (MedInfoSys).
- All field staff had been briefed on how to handle all enquiries (including tapentadol) so as to route these through a written 'request for information' from health professionals or appropriate administrative staff and signed by those health professionals or appropriate administrative staff. Grünenthal provided certified briefing materials. All requests for information were recorded and tracked in MedInfoSys.
- Upon request from the MHRA, a specific request for information system for budget holders/policy maker enquiries was established. Prior to this the existing request for information system was in place at all times.
- During enquiries related to collecting information on formulary systems and protocols for new medicines, some budget holders/policy makers requested specific budgetary information about tapentadol from a HELM. The appropriate medical information response was clearly outlined in the briefing to the HELM team on the 28 April 2010 (provided) after obtaining final clarification with the MHRA.
- The MHRA also required that all other tapentadol advertising and promotional materials related to tapentadol should be reviewed by the MHRA before use. Grünenthal had agreed to this.

Grünenthal provided a copy of the HELM job description and submitted that essentially, this was a non-promotional role to help budget holders/policy makers plan for the inclusion of Grünenthal products within their locality. Grünenthal also provided the briefing instructions for the HELMs, which it submitted emphasized the importance of not proactively raising tapentadol: -

a) 4 February 2010 – 1st Joint Health Economic Liaison Managers Meeting – another pharmaceutical company/Grünenthal. By way of an explanation:
   i) Slide 38 referred to MOR-NRI (the mode of action of tapentadol). The verbal briefing referred to post licence work as this slide set covered all strategic and tactical elements of the launch programme. No HELM pre-launch MOR-NRI materials were approved for use.
   ii) Slide 43 referred to 'Raise awareness of Palexia' – this was part of the post licence strategy and clearly a critical success factor in its commercialization.
   iii) Slide 69 set out annual contacts related to account mapping with payers. This was not related to MOR-NRI or product but looked at cost containment in pain related matters. Grünenthal focused on pain management.
   iv) Slide 82 referred to HELM clinical contacts. HELM did not meet clinicians per se but some budget holders/policy makers had clinical attachments. HELMs were instructed that where a clinical question arose, to raise a request for information, which could lead to a medical science liaison (MSL) visit if the clinician so wished.

b) 2 March 2010 – 2nd Joint Health Economic Liaison Mangers Meeting – another pharmaceutical company/Grünenthal (documents provided). An advanced notification documentation in draft form was reviewed but never used – slides were attached. Key business question 1 (KBQ1) referred to ladders of adoption as part of the 'Tapentadol Road Map' - aimed at identifying accounts and processes for formulary applications.

c) Grünenthal was in an ongoing dialogue with the MHRA from January 2010. This finally resulted in a meeting with the MHRA on 31 March 2010. A HELM briefing meeting (documents provided) was subsequently held on 28 April 2010, which was consistent with the final MHRA letter dated 29 April 2010.

   The slides 'Palexia Market Access Plan' (provided) covered the current HELM activity with timelines for tapentadol activity (text in red) after the anticipated marketing authorization date in September (slides 14,15) and contingencies to adjust dates should the marketing authorization dates change (slide 16).

   The slides 'Materials' (provided) looked at Versatis cost-efficacy considerations, and account mapping. HELMs were directed to send a request for information to medical information in the event that questions were asked about any products. The request must be specific about the product in order that medical information could answer specifically.

d) Belfast company meeting - (documents provided)

e) Request for information, May HELM briefing – (documents provided)

Grünenthal' submitted that HELMs were trained to undertake account mapping for the future formulary inclusion of tapentadol. This was outlined in a series of briefing presentations to the HELM team (see above) as to how they should engage with customers. Following Grünenthal's final dialogue with the MHRA in April 2010, its brief from the ruling was to engage with budget holders/policy makers only to establish the process by which new products in general might be submitted for local drug and therapeutic committee review.

Grünenthal' stated that HELMs did not proactively contact health professionals or appropriate administrative staff about tapentadol and they had no materials. HELMs proactively contacted budget holders/policy makers about:

a) Versatis budgetary implications.
b) Formulary/account mapping.
c) 'Change Pain', an educational disease awareness programme tailored to each customer group to explore the problems of pain management in general and costs to society. It was also part of Grünenthal's vision of establishing the company's pain management focus in partnership with healthcare systems.
d) Contrary to the complaint, HELMs had no tapentadol materials or slide sets to use in discussions with budget holders/policy makers. HELMs did not proactively see anyone about tapentadol.

Grünenthal submitted that it routinely recorded the number of customers seen by HELMs. The company expected the HELM team to spend broadly 40% of its time working on Versatis formulary activity, and 60% between 'Change Pain' and formulary activities/account mapping. The company did not set call targets apart from a generic expectation of maintaining an industry average of 2 calls per day. There were no written instructions or briefing materials related to call rates.

Grünenthal submitted that subject to the comment directly below, no Grünenthal staff called upon health professionals or appropriate administrative staff about tapentadol proactively and there were no proactive materials available for tapentadol.

Medical information triaged all enquiries. This resulted in a response to the enquirer using a verbal response and/or a standard (approved) letter where applicable. All was logged in MedInfo Sys. Where a request was made for a member of the medical department to present information on tapentadol, an MSL might call. MSLs were all PhD scientists with a background in neuroscience or a related area. There was a MOR-NRI approved slide set and a tapentadol approved slide set which were only shown on specific request. These slide sets and certification forms were provided.

As from 29 January 2010, Grünenthal had run discrete advisory boards which were an essential preparatory part of understanding a disease area, were not promotional and were an accepted way of gauging external environment and future opportunities. Also, the agenda and interactive nature of the meetings were made clear (eg 18 March 2010 meeting), the number of attendees was limited and honoraria paid was not disproportionate given the standing of the invited attendees and input expected from them. These meetings sought advice on the development of tapentadol, line extension, commercial positioning and messaging, and health technology appraisals. All had been certified. All were subject to confidentiality agreements and service contacts and a customary fee was paid to members of the advisory board. Details were given below, and copies of the agendas and certificates were provided.

a) 18 March –Task Force advisory board (17 national clinical leaders in pain management – data review and advice on the communication of tapentadol's unique mode of action), London.
b) 30 May – Round Table – a special interest group on neuropathic pain (NeuPSIG) (5 clinical pain specialists – advice on neuropathic pain management) Athens.
c) 24 June 2010 –Task Force advisory board (16 attendees – advice on positioning of tapentadol in a pain management algorithm), London.

d) 30 June 2010 – Mock drug and therapeutic committee application advisory board (9 clinicians and budgetary influencers – advice on how to construct an application) Stokenchurch, Head office.
e) Media Task Force – media clinicians advisory board on communicating pain information in the media – to come.

Grünenthal noted that the complainant referred to contacting 3,000 health professionals. Grünenthal submitted that the issue was dealt with to the satisfaction of the MHRA and appropriate procedures had now been put in place.

Grünenthal submitted that since 29 January 2010, no health professionals or appropriate administrative staff had been contacted in a similar manner as was the substance of the MHRA complaint (ie a proactive advance notification letter).

Grünenthal submitted that it had at all times maintained high standards, had not brought discredit to or reduced confidence in the industry and in particular had not promoted an unlicensed medicine. High standards had been maintained and, therefore, Grünenthal was not in breach of Clause 9.1. Promotion had not occurred before the marketing authorization of tapentadol and Clause 3.1 had not been breached following the MHRA initial review. Finally, following MHRA guidance, Grünenthal had complied in every way with Clause 2.

As stated above, with a view to ensuring its continuing compliance, Grünenthal had submitted to the pre-vetting of promotional materials for tapentadol.

Finally, Grünenthal submitted that it was very concerned that this was an anonymous complaint unaccompanied by evidence. Grünenthal trusted the Panel would view this complaint in context; the burden of proof should lie with the complainant and its evidence, of which there was none. Nevertheless, until this complaint was resolved, only medical information would respond to enquiries, even if an MSL or HELM visit had been requested or was pending.

In response to a request for further information, Grünenthal explained that the HELMs were informed of the action taken by the MHRA and the subsequent changes they would have to make to what they did and said with regard to tapentadol in face-to-face meetings. These meetings were held to update staff on the progress and issues with regard to the ongoing dialogue with the MHRA through January to April 2010. It was explained that the MHRA had queried the company's procedures with regard to advanced notification for tapentadol. The briefing slides used during this period were provided; no additional written instructions were issued. Meetings were held with the HELM team on 4 February, 2 March and 28 April 2010.

At the meetings in February and March, the HELM team was clearly instructed to follow the existing Grünenthal request for information process (as outlined above) for unsolicited customer enquiries and discussion about tapentadol. Thus any spontaneous queries about tapentadol were sent to medical information for action.

Grünenthal stated that the HELMs had not engaged in any pro-active advanced notification for tapentadol following the company's agreement with the MHRA on 29 January. All requests for information for tapentadol by health professionals had been processed through the request for information process via the medical information department.

The HELM team had engaged in a formulary mapping exercise to gain an understanding of how a new medicine would be introduced in the local health economy. This process was outlined in briefing documents provided. No pro-active engagement of payers or other NHS employees had been undertaken following the company's agreement with the MHRA on 29 January. Any customer that spontaneously raised the topic of tapentadol with a HELM after 29 January would have been asked to complete a request for information form which would have been sent to the medical information department for action.

The HELMs were not given materials about tapentadol because as outlined above, no agreement was reached with the MHRA about the use of an advanced notification document.

The HELMS were instructed to use the existing request for information process for all products in June 2009 via a presentation at their monthly meeting. At the meeting on 4 February this process was reinforced. At the 28 April meeting the specific tapentadol request for information process was introduced and the HELMs instructed on its use. No written instructions were issued as effective communication was achieved verbally at the monthly meetings.

Grünenthal submitted that after it had been notified by the Authority on 28 June of this complaint all formulary mapping activities were suspended. The written briefing informing the HELMs of this was provided.

In response to a further request for more information, Grünenthal explained that the HELMs were verbally briefed at the meeting on 4 February that the company was in dialogue with the MHRA with regard to its activity for advance notification. The HELMs were instructed to ensure that they used the Grünenthal request for information process for any spontaneous questions on tapentadol and not to engage customers with proactive questions about the product during the period when the company was seeking clarification of what advance notification materials and process the MHRA would allow under its rules. As this matter was outlined in the MHRA Blue Book and the Code, the company was seeking to understand what it could undertake following discussion with the MHRA.

Grünenthal submitted that the slides used at the briefing meeting on 4 February were not modified as it believed it had a robust process in place for request for information queries through medical information for questions on tapentadol from heath professionals.

Grünenthal stated that given that the advance notification process was under review, at the HELMs briefing meeting in March it explored possible solutions bearing in mind the lack of an agreed way forward with MHRA at that point. Grünenthal did not get final resolution of this issue until its final correspondence with the MHRA on the advanced notification process in April when the MHRA indicated that it was not happy with any of Grünenthal's materials or process. Therefore, Grünenthal informed the HELMs of this and implemented the specific HELM request for information outlined above which did not involve any proactive discussion of tapentadol with health professionals.

Grünenthal explained that the formulary mapping exercise required HELMs to seek answers to a number of key business questions with regard to the decision making process in the local health care economy. The slide presentation, already provided, detailed the questions the HELMs were expected to answer to the best of their knowledge following the data mapping exercise.

The formulary mapping exercise was designed as a data collection process rather than a data giving process, ie the HELMs did not impart information but gathered it in relation to the local health economy's process; local arrangements could differ substantially. The answers to the key business questions were for internal use to appropriately prepare the organization for engaging with payer customers and healthcare systems when the marketing authorization was received.

Grünenthal had a business need to map local processes involved in getting a new product on formulary. The questions outlined were for the HELMs. They must gather information appropriately to answer these questions where possible.

This process was distinct from a proactive advance notification process undertaken by pharmaceutical organizations in response to the payer customers in the NHS needing to be prepared for the introduction of a new product and allowed under the Code.

Grünenthal explained that the HELMs visited individuals who were responsible for the approval and purchase of medicines within the NHS. They also visited those who had to gain approval for the use of medicines in the various local health economies across the country. The HELMs saw both types of customers on matters related to Grünenthal's licensed products in a proactive manner. These meetings were booked in a standard way with the HELM contacting individuals with regard to discussions on marketed pain products. Where HELMs had existing relationships with payer customers they had gathered an understanding about local formulary systems in relation to the introduction of new medicines.

The HELMs were instructed to say nothing about tapentadol and to use the request for information process for information requests through medical information department. They had not been issued with materials on tapentadol.

The mapping process required the HELM to answer a series of questions in relation to local formulary and access in preparation for the launch of a new product. These questions were a guide to aid the HELM in describing to Grünenthal how the local payer process worked and where, in this case, tapentadol might fit.

As tapentadol had been commercially available in the USA for over a year, a number of scientific papers had appeared in the medical press and such data had been presented at international scientific meeting it was not unexpected for some UK health professionals to know about tapentadol and that spontaneous questions might arise.

In summary, Grünenthal from the beginning of February 2010 had sought to comply with the recommendations on activities for advance notification with the MHRA. Being unable to resolve this process following a review based on the MHRA dialogue it stopped all advanced notification activities.

As part of Grünenthal's internal business planning process the HELMs were asked to answer a series of key business questions. This was outlined in a series of slides used to brief the team. Information on the local formulary process was collated by the HELMs from data gathering interactions with local payers. Grünenthal had suspended all formulary mapping activity following receipt of this complaint.

Grünenthal considered that it needed to ensure a clear distinction between activities related to advance notification for tapentadol, where activities were suspended at the end of January and formulary mapping activities to inform local business planning for successful market access post marketing authorization which were suspended pending resolution of this complaint.

PANEL RULING

The Panel noted that the complaint from an anonymous source to the MHRA was that Grünenthal continued to promote tapentadol prior to the grant of a marketing authorization. The MHRA had received a complaint about the matter in November 2009 and had agreed action with Grünenthal in January 2010; the case report was published in March 2010. The Panel noted that the MHRA had considered the activities in relation to the Advertising Regulations and the Blue Guide. The Panel considered that it was limited to considering Grünenthal's activities after January 2010 in relation to the Code.

The Panel noted Grünenthal's comments about the anonymous source of the complaint to the MHRA and the burden of proof. The Panel noted, as set out in the introduction to the Constitution and Procedure, that complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties.

The Panel noted that Grünenthal anticipated that tapentadol would be granted a marketing authorization in September 2010.

The supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes, stated that health authorities and health boards and their equivalents, trust hospitals and primary care trusts and groups needed to establish their likely budgets two to three years in advance in order to meet Treasury requirements and there was a need for them to receive advance information about the introduction of new medicines, or changes to existing medicines, which might significantly affect their level of expenditure during future years. It was noted that when this information was required, the medicines concerned would not be the subject of marketing authorizations (though applications would often have been made) and it would thus be contrary to the Code for them to be promoted. The supplementary information gave guidance on the basis on which such advance information could be provided including the requirement to include the likely cost and budgetary implications which must make significant differences to the likely expenditure of heath authorities etc.

The Panel noted that Grünenthal had begun an advance notification process for tapentadol in November 2009 ie only 10 months before it anticipated having a marketing authorization for the medicine. In that regard, the Panel queried whether the information had been supplied early enough such that budget holders etc could be reasonably expected to act upon it.

Information could only be supplied if the product had a significant budgetary implication. The Panel queried whether the introduction of tapentadol would have a significant budgetary implication but did not consider this was relevant to the complaint before it.

The Panel disagreed with Grünenthal's submission that the HELM position was a non-promotional role. The job description for the HELMs stated 'The aim of these positions will be to address barriers to access for specific products and increase sales of existing products by identifying prescribers, influences and decision making groups that have an influence on current provision of healthcare'. Under the heading 'Overall Purpose of the Role' reference was made to increasing patient access to Grünenthal products, maximising product usage, formulary inclusions, formulary status and ensuring patient access to Grünenthal products. HELMs were expected to have 'Selling skills with emphasis on payer NHS focus' and to 'Demonstrate ability to sell at all levels with the proven ability to overcome barriers'. They were required to have passed the ABPI Medical Representatives Examination. The heading 'Responsibilities of Job/Limits of Authority' included 'Develop and maintain knowledge of disease area, products and health economic cases for products and competition' and 'Work closely with the company's sales, health policy and head office teams to ensure access to Grünenthal products is optimal'.

The job description did not specifically refer to the HELMs' role with regard to advance notification, nor did it clearly state that it was a non-promotional role. In the Panel's view, and contrary to Grünenthal's submission, the job description described a promotional role.

The Panel noted that the HELMs had been briefed on 28 April 2010 with a presentation entitled 'Materials'. Slide 6, headed 'Portfolio Approach' stated, as the third bullet point, 'Basic tapentadol information can be given verbally'. Slide 8 'Product Specific Information' stated the following:

- 'Questions of a substantive nature relating to tapentadol must go via Medical Information.
- The response to these questions can be delivered by appropriately trained staff.
- Therefore, in compliance with the MHRA's request, materials available do not refer to tapentadol.'

It appeared, therefore, that whilst HELMs were not given any printed material regarding tapentadol, they could still talk about it. The Panel considered that this approach was wholly unacceptable. There was no guidance as to what constituted 'Basic tapentadol information' or 'Questions of a substantive nature'. Slide 9 headed 'Basic information: What can I say?' listed the permitted basic information namely the name of the products in the portfolio, when they would be available, what was or would be their indication and or cost and what was the value of the product. Slide 10 was headed 'Further questioning which may assist in helping address the KBQs [key business questions] and map the account'. They were divided into two areas 'process' and 'clinical'. The process section included questions about local protocols/guidelines and likely reaction of medicines management. The clinical section included a question about which clinical areas could the product be used in and which current therapies could the product challenge. It included the statement 'Any further requests for product specific information should be sent to Med Info via the [request for information]'. The Panel further noted that slides 13 and 14 headed 'What does tapentadol offer over existing therapies in Med Info Response' appeared to reproduce the text of a medical information letter and some bar charts which compared tapentadol with oxycodone. Although both slides were marked 'Example – not approved for distribution' there was no instructions as to whether the information could be delivered verbally by the HELMs as basic tapentadol information. The Panel was very concerned that material showing an advantage for tapentadol PR over oxycodone CR had been shown to the HELMs. At a previous meeting, 4 February, HELMs had been shown the core messages for Palexia. In the Panel's view, the more information the HELMs were given about tapentadol the more likely they were to use it to 'overcome barriers' and 'ensure patient access'.

The Panel noted Grünenthal's submission that the HELMs had not engaged in any proactive advance notification for tapentadol following an agreement with the MHRA on 29 January. It appeared that since

then the HELMs had undertaken a formulary mapping exercise to gain an understanding of how a new medicine would be introduced into the local health economy. This exercise required the HELMs to seek answers to a number of key business questions. Some of those questions were detailed in a briefing presentation, 2 March and included the following: 'Identify attitudes to [controlled drugs] and tapentadol in nociceptive neuropathic and specifically back pain'; 'Where do they see tapentadol on the analgesic ladder?'; 'Where does the customer see a new pain drug adding most value?' and 'Does [drug and therapeutics] need to be achieved before a new pain drug can be used?'. The Panel noted Grünenthal's submission that following dialogue with the MHRA in April 2010, HELMs were briefed to discuss the process issues in relation to new products in general. Further formulary mapping questions appeared in the presentation dated 28 April 2010 described above.

The Panel noted that the HELMs visited individuals responsible for the approval and purchase of medicines within the NHS; they also visited those who had to gain approval for the use of medicines in local health economies. The HELMs proactively saw both types of customers in relation to Grünenthal's licensed products (Tramacet, Versatis and Zydol) all of which were for pain relief. The Panel considered that in this regard customers would see the HELMs as medical representatives. To have that same group of people then asking questions about tapentadol or a 'new pain drug' would be seen as promotional. The Panel noted its comments above regarding the selling skills of the HELMs.

The Panel considered that the HELMs' role was not non-promotional. Their activities were not limited to a fact finding role as the nature of the questions they were to ask would raise interest and awareness in the new product and solicit questions about it. The slides presented to the HELMs about tapentadol reinforced the promotional aspect of their activity. The HELMs were expected to have selling skills and they visited the same people to tell them about licensed medicines and to ask them questions about tapentadol and/or 'a new pain drug'. In the Panel's view asking such questions amounted to the promotion of tapentadol before the grant of its marketing authorization. Thus a breach of Clause 3.1 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 of the Code was a sign of particular censure and reserved for such. The supplementary information to that clause listed examples of activities likely to be in breach of Clause 2 and included promotion prior to the grant of a marketing authorization. The Panel considered that to brief a team, employed for its selling skills, to raise the profile of tapentadol and/or 'a new pain drug' just weeks before the expected grant of a marketing authorization was unacceptable. The Panel was very concerned about the failure to provide the HELMs with clear written instruction and this was a particularly serious omission given the concerns raised by the MHRA about the activity. The Panel considered that the activity amounted to a softening of the market. Such activity brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned about Grünenthal's activities with regard to the advanced notification of tapentadol. The MHRA had provided advice to the company following a mailing about tapentadol to 3,000 people. Since being in correspondence with the MHRA, Grünenthal had used a team of HELMs to gather information about, inter alia, attitudes to tapentadol and how to get 'a new pain drug' on to a formulary. The HELMs were expected to have selling skills and saw some of the same people about licensed and unlicensed medicines. The HELMs were expected to work closely with the sales team. Briefings to HELMs about this matter after the intervention of the MHRA were inadequate. Overall the Panel considered that Grünenthal's activity amounted to the promotion of tapentadol prior to the grant of its licence. In the Panel's view the HELMs' activities did not constitute the advance notification of tapentadol as no information was being supplied that showed that the product would have a significant budgetary effect. The Panel considered that overall Grünenthal's actions were unacceptable. The Panel decided to report the company to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. The Panel noted Grünenthal's submission that on receipt of this complaint it had suspended all formulary mapping activities.

COMMENTS FROM GRÜNENTHAL ON THE REPORT

At the consideration of the report the representatives from Grünenthal apologised and accepted that there had been failings that had led to the Panel's rulings. It was difficult for the company to prove what was done (and what was not done) in the absence of evidence. The HELM briefing slides had not been properly checked/approved and had failed to state what could not be done. The representatives stated that in order to avoid similar breaches of the Code in the future it had: put in place new policies, procedures and structures; updated the HELMs' job description; retrained final signatories; introduced an electronic approval system; proposed the appointment of a Code compliance manager; updated all Code related standard operating procedures; arranged an audit by external consultants; reviewed all HELM material and disciplining action for relevant staff was under way.

APPEAL BOARD CONSIDERATION

The Appeal Board noted from the company representatives that Grünenthal had originally set up a market access team comprised of two managers and five HELMs to try to limit the extensive off-label use of Versatis and to gain market access for its portfolio of licensed pain medicines. Part of the HELMs' role was to promote Grünenthal's medicines. The company had then used this same team, with the same job description, to work on the advance

notification of tapentadol. In response to a question the representatives described the reasons why the company considered that the introduction of tapentadol would have a significant budgetary impact. The Appeal Board was very concerned about the conduct of Grünenthal. The prohibition on the promotion of a medicine prior to the receipt of its marketing authorization should have been well understood by the two senior managers representing the company who themselves had referred to their many years of experience in the industry. In that regard the deployment of the HELMs to work on the advance notification of tapentadol should have been tightly controlled from the outset. Even in the absence of this, it appeared that Grünenthal had not taken the opportunity to thoroughly review the HELMs' role and responsibilities when the MHRA had determined that, in providing advance notification, they had infact promoted tapentadol prior to the grant of its marketing authorization. Although changes had been made to the way the HELMs worked at this point, in that they had no role in relation to advance notification, the account mapping and other activities which they carried out were considered by the Panel to still amount to the promotion of a medicine prior to the grant of its marketing authorization. This was unacceptable.

The Appeal Board was very concerned to learn that the market access team had generated presentations and briefing materials for the HELMs which had not been certified. In that regard the Appeal Board queried whether the senior management team had exercised sufficient control over the market access team especially considering it was newly appointed, had responsibilities for an unlicensed medicine and the MHRA's involvement in the matter.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of Grünenthal's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

FURTHER APPEAL BOARD CONSIDERATION

Upon receipt of the audit report (October 2010) the Appeal Board noted that Grünenthal had agreed compliance plans which would address all the areas recommended for attention and this was already being implemented.

The Appeal Board decided that a second audit should be carried out in February 2011 when it would expect the recommendations in the audit report to be implemented. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the second audit report (delayed until March 2011) the Appeal Board was encouraged by Grünenthal's progress since October but considered that the company still needed to demonstrate that it understood the importance of compliance. The Code and its requirements needed to become embedded into all levels of the company.

The Appeal Board decided that a third audit should be carried out in September when it would expect the recommendations in the audit report to be implemented. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon consideration of the third audit the Appeal Board was concerned that it still appeared that the company had not really understood the seriousness of the situation. The Appeal Board was extremely concerned to note errors in the response from Grünenthal to the recommendations from the March 2011 audit (part of the preparation for the September 2011 audit). This was unacceptable. It was hard to believe, given the recommendation in March that the company should be confident that all the Versatis material was clear regarding the licensed indication, that the company had not been precise about what had been done. Senior employees had not taken decisive action to implement the recommendation. The failure of senior employees to respond in full to questions at the audit about that recommendation led the Appeal Board to question the company's stated commitment to compliance.

The Appeal Board decided that, in accordance with Paragraph 11.3 of the Constitution and Procedure, Grünenthal should be publicly reprimanded in relation to the misinformation in its response to the Authority. Prior to the third audit the Appeal Board was extremely concerned about the apparent lack of demonstrated change in the company culture. It noted that some activities had been started and these might improve the situation. A new general manager was appointed in October. The Appeal Board decided that a fourth audit of Grünenthal should take place by mid February 2012. Upon receipt of the report for that audit, it would decide whether further action was needed.

Upon consideration of the fourth audit report the Appeal Board noted that Grünenthal had undergone changes in senior staff including a new general manager. There appeared to be a different culture in the company and a more positive attitude to compliance. The Appeal Board considered that there had been encouraging progress since the last audit. On the basis that the company adopted an approach of continual improvement the Appeal Board considered that no further action was required.

Complaint received	**25 June 2010**
Undertaking received	**7 September 2010**
Appeal Board consideration **22 September 2010, 10 November 2010,** **28 April 2011,16 November 2011, 22 March 2012**	
Interim case report published	**4 November 2010**
Case completed	**22 March 2012**

CASE AUTH/2442/10/11

PHARMACOSMOS/DIRECTOR v VIFOR

Breach of undertaking

Pharmacosmos AS alleged that Vifor Pharma UK had breached its undertaking given in Case AUTH/2422/7/11 by using the claim 'Ferinject avoids dextran-induced hypersensitivity reactions' in two press releases which were available on the company's website in October 2011. Pharmacosmos noted that the claim had been ruled in breach of the Code because it wrongly implied that Ferinject was free of hypersensitivity reactions. The undertaking given in Case AUTH/2422/7/11 was dated 30 August 2011.

One press release, dated 13 June, was about the approval by the Scottish Medicines Consortium (SMC) for the use of Ferinject for the treatment of iron deficiency anaemia. The other was about the Medicines and Healthcare products Regulatory Agency (MHRA) approval for a simplified dosing regimen for the treatment of iron deficiency.

The case was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

The detailed response from Vifor 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.

In Case AUTH/2422/7/11 the claim at issue, 'Ferinject avoids dextran-induced hypersensitive reactions' had appeared in a leavepiece. In that case, the Panel noted that Section 4.4 of the Ferinject SPC, Special warnings and precautions for use, stated that 'Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be potentially fatal …. Therefore, facilities for cardio-pulmonary resuscitation must be available'. Section 4.8, Undesirable effects listed hypersensitivity including anaphylactoid reactions as an uncommon side effect. The only reference to this possible side effect to Ferinject in the leavepiece at issue was in the prescribing information. The Panel did not accept Vifor's submission that the prescribing information on the back page of the leavepiece provided all the relevant safety information about hypersensitivity reactions. Claims in promotional material had to be capable of standing alone without reference to, *inter alia*, prescribing information to correct an otherwise misleading impression.

The Panel did not accept Vifor's submission in Case AUTH/2422/7/11 that the potential for hypersensitivity reactions with Ferinject *per se* was a separate issue. The claim at issue highlighted the issue of hypersensitivity reactions and in the Panel's view, without a counter-balancing statement with regard to the possibility of hypersensitivity reactions with Ferinject, sought to minimise the prescriber's concerns about such reactions and in that regard might compromise patient safety. A breach of the Code was ruled.

Turning to Case AUTH/2442/10/11, the Panel considered that the claim that Ferinject was '…not associated with dextran-induced hypersensitivity reactions' in the MHRA approval press release was covered by the undertaking in Case AUTH/2422/7/11 although unlike the leavepiece, the press release was not aimed solely at prescribers. The claim highlighted the issue of hypersensitivity reactions and in the Panel's view, without a counter-balancing statement with regard to the possibility of hypersensitivity reactions with Ferinject, sought to minimise the concerns about such reactions. A breach of the Code was ruled as acknowledged by Vifor.

Although the claim in the SMC approval press release that Ferinject was '…not associated with dextran-induced hypersensitivity reactions since it is free of dextran and dextran derivatives…' gave more details it again implied that there was no need to be concerned about hypersensitivity reactions with Ferinject. In the Panel's view this was similarly covered by the undertaking in Case AUTH/2422/7/11. A breach of the Code was ruled as acknowledged by Vifor.

The Panel considered that high standards had not been maintained and ruled a breach of the Code. The Panel considered that failing to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Pharmacosmos AS alleged that Vifor Pharma UK Limited had breached its undertaking given in Case AUTH/2422/7/11 in which the claim 'Ferinject avoids dextran-induced hypersensitivity reactions' in a leavepiece was ruled in breach of the Code. The undertaking given in that case was dated 30 August 2011. The material now at issue was two press releases on the Vifor UK website.

The case was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

COMPLAINT

Pharmacosmos provided screen shots of the Vifor UK website taken on Tuesday, 4 October. Two press releases on the website included the claim at issue in a paragraph of supporting information headed

'About Ferinject'. Pharmacosmos noted that the claim had been ruled in breach of the Code because it wrongly implied that Ferinject was free of hypersensitivity reactions.

A press release dated 13 June about the approval by the Scottish Medicines Consortium (SMC) for the use of Ferinject in the treatment of iron deficiency anaemia stated:

> 'Ferinject is an innovative I.V. iron replacement product discovered and developed by Vifor Pharma. Ferric carboxymaltose, the active pharmaceutical ingredient of Ferinject, overcomes the unmet clinical needs of I.V. iron therapy as Ferinject is not associated with dextran-induced hypersensitivity reactions since it is free of dextran and dextran derivatives, and has a low potential for iron toxicity. Ferinject, in doses up to 1000 mg iron, can be administered in a 15 minute drip infusion in patients with iron deficiency associated with a variety of clinical conditions.'

A September press release about the Medicines and Healthcare products Regulatory Agency (MHRA) approval for a simplified dosing regimen for the treatment of iron deficiency stated:

> 'Ferinject is an innovative intravenous iron replacement product discovered and developed by Vifor Pharma. Ferric carboxymaltose, the active pharmaceutical ingredient of Ferinject, meets the unmet clinical need for an intravenous (I.V.) iron therapy that is not associated with dextran-induced hypersensitivity reactions with a low iron toxicity potential. Ferinject can be administered in doses up to 1000mg iron in a 15-minute drip infusion or I.V. injection in patients with iron deficiency associated with a variety of clinical conditions.'

On the basis of the above, Pharmacosmos alleged a breach of Clause 25.

When writing to Vifor, the Authority asked it to consider the requirements of Clauses 2 and 9.1 in addition to Clause 25 as cited by Pharmacosmos.

RESPONSE

Vifor submitted that following Cases AUTH/2422/7/11 and AUTH/2423/7/11 the leavepieces at issue (refs 0148/FER/2011 and 0090A/FER/2011 respectively) were withdrawn as per the undertakings given. This resulted in almost all of the promotional material used by the sales teams, 58 different items, being withdrawn from circulation on 31 August 2011 in line with the company's standard operating procedure (SOP) for the withdrawal of promotional material (a list of the materials withdrawn was provided). Vifor submitted that this process meant that there were no new materials available to order. Additionally, all the materials that were held by the sales teams were collected and destroyed according to the SOP for the withdrawal of promotional material.

A new sales aid and four further leavepieces which did not include the claims at issue were sent to the sales teams on 22 September 2011 and had been used ever since. As a consequence of the two cases, Vifor undertook a comprehensive review of all of its materials in addition to the approval and withdrawal processes.

As this review was undertaken solely on materials in circulation, the two press releases that were prepared globally for two important company announcements were, unfortunately, missed. Vifor acknowledged this oversight and noted that as soon as the matter was brought to its attention, it withdrew the press releases from its website.

The two press releases in question were signed off before the claims were ruled in breach of the Code and before the undertaking given on 30 August 2011. The SMC approval press release was approved for release on 13 April 2011 and the MHRA approval press release was approved for release on 13 July. The claims at issue were part of the press release boiler plate provided to affiliates by Vifor Pharma International. The boiler plate had since been changed and a new one that did not include the claim at issue had been given to all Vifor Pharma affiliates.

Despite the press release on the revised Ferinject summary of product characteristics (SPC) being approved on 13 July, it was only posted on the Vifor website on 7 September, the day the new SPC was available in the UK. Vifor noted that the press release was not prepared or approved after the undertaking was given.

Nonetheless, Vifor acknowledged that not checking the press release was an oversight on its part which it regretted and for which it apologised. However, this oversight notwithstanding, it submitted that comprehensive steps were followed at considerable cost to the company in order to comply with the undertaking given in Case AUTH/2422/7/11.

Vifor stated that it had since added an additional step in its SOP for the withdrawal of promotional material in order to ensure this did not happen again.

In response to a request for clarification regarding the date of issue of the two press releases Vifor stated that the SMC approval press release was signed off on 13 June 2011. It was distributed on 13 June to the medical media by a public relations agency. A distribution list was provided. It was put on the Vifor UK website on 14 June and as a result of the breach was taken off the website on 12 October 2011. The date of 13 April above was a typing error and Vifor apologised for the confusion caused.

With regard to the MHRA approval press release Vifor explained that the MHRA was the reference member state for Ferinject. When the MHRA approved the label changes in July 2011, a press release was prepared to communicate the information globally.

The MHRA approval press release was approved for media release on 13 July 2011. The approval was via email as the signatories were not available in the office and a copy of the electronic approval was added to the job bag. As the Vifor signatories were out of the office on 13 July the job bag itself was therefore not physically signed off until 21 July 2011 and 4 August respectively, by the two final signatories. This press release was distributed on 13 July to the medical media by Vifor's public relations agency which released it via email to the same distribution list as for the SMC approval press release.

After several minor iterations, the final wording of the UK SPC reflecting the full MHRA label update was made available to Vifor Pharma UK from Vifor global regulatory in early September 2011. The global press release was therefore placed on the Vifor UK website on 7 September 2011 and when the company realised it was in breach it was taken off the website on 12 October 2011.

There had been a subsequent further variation to the Ferinject SPC that came into effect on 29 September 2011 and so a revised version of the Ferinject SPC was issued on 29 September. The current SPC was supplied to the Authority as requested, ie the 29 September 2011 version.

PANEL RULING

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.

Case AUTH/2422/7/11

The material at issue in this case was a claim in a leavepiece (ref 0148/FER/2011) that 'Ferinject avoids dextran-induced hypersensitive reactions'. The claim appeared as the second bullet point in a section headed 'How quickly can Ferinject be administered?'.

The Panel noted that Section 4.4 of the Ferinject SPC, Special warnings and precautions for use, stated that 'Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be potentially fatal …. Therefore, facilities for cardio-pulmonary resuscitation must be available'. Section 4.8, Undesirable effects listed hypersensitivity including anaphylactoid reactions as an uncommon side effect. The only reference to this possible side effect to Ferinject in the leavepiece at issue was in the prescribing information. The Panel did not accept Vifor's submission that the prescribing information on the back page of the leavepiece provided all the relevant safety information about hypersensitivity reactions. Claims in promotional material had to be capable of standing alone without reference to, *inter alia*, prescribing information to correct an otherwise misleading impression.

The Panel did not accept Vifor's submission that the potential for hypersensitivity reactions with Ferinject *per se* was a separate issue. The claim at issue highlighted the issue of hypersensitivity reactions and in the Panel's view, without a counter-balancing statement with regard to the possibility of hypersensitivity reactions with Ferinject, sought to minimise the prescriber's concerns about such reactions and in that regard might compromise patient safety.

The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The case had also involved another claim which the Panel considered was misleading with regard to adverse events. The Panel considered that both of the claims at issue would minimise a prescriber's concerns about Ferinject's safety profile and as activities which were prejudicial to patient safety were regarded as serious matters it reported Vifor to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. The Appeal Board decided that Vifor should be audited and following receipt of the audit report the Appeal Board would consider whether further action was necessary.

Case AUTH/2442/10/11

Turning to the case now before it, the Panel noted that the material at issue was two press releases. The SMC approval press release had been signed off on 13 June 2011 according to the 'Job Bag Item Approval Form' and the form stating that the material was 'Approved as compliant with Vifor Pharma Policies and SOPs and with the requirements of the ABPI Code of Practice for the Pharmaceutical Industry 2011' and not 13 April as stated in Vifor's first response. This apparent inconsistency was followed up with Vifor which acknowledged that its first submission included a typographical error and the SMC approval press release was signed off on 13 June. It had been published on the Vifor website on 14 June 2011. There was no reference on the SMC approval press release provided by Vifor unlike the certificate which bore the reference 0229A/FER/2001. The reference did appear in the version provided by Pharmacosmos.

The second press release was dated 13 July 2011 and referred to the MHRA approval. The certificate bore the reference 0265/FER/2011 and according to the documentation it was signed off on 21 July and 4 August as being compliant with Vifor Policies, SOPs and the Code. The final sign off of the job bag approval form was dated 21 July and not 13 July as stated in Vifor's first response. The Panel noted that Vifor's second submission explained that the MHRA approval press release had been approved by email and the job bag had been signed when the signatories were next in the office. The Panel noted that the MHRA press release was placed on the Vifor website on 7 September.

The Panel considered that the claim that Ferinject was '…not associated with dextran-induced hypersensitivity reactions' in the MHRA approval press release was covered by the undertaking in Case AUTH/2422/7/11 although unlike the leavepiece,

the press release was not aimed solely at prescribers. The claim now at issue highlighted the issue of hypersensitivity reactions and in the Panel's view, without a counter-balancing statement with regard to the possibility of hypersensitivity reactions with Ferinject, sought to minimise the concerns about such reactions. A breach of Clause 25 was ruled as acknowledged by Vifor.

Although the claim in the SMC approval press release that Ferinject was '…not associated with dextran-induced hypersensitivity reactions since it is free of dextran and dextran derivatives…' gave more details it again implied that there was no need to be concerned about hypersensitivity reactions with Ferinject. In the Panel's view this was similarly covered by the undertaking in Case AUTH/2422/7/11. A breach of Clause 25 was ruled as acknowledged by Vifor.

The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. Failing to comply with an undertaking and assurance was cited as an example of an activity likely to be in breach of Clause 2. The Panel considered that failing to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **11 October 2011**

Case completed **18 November 2011**

CASE AUTH/2444/10/11

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

Pradaxa website

A general practitioner complained about a Pradaxa (dabigatran) website created by Boehringer Ingelheim.

The complainant questioned whether access to the medical content for health professionals was sufficiently rigorous to restrict access only to health professionals. The complainant alleged that the arrangements were such that Boehringer Ingelheim clearly intended to facilitate the promotion of Pradaxa to the public.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that supplementary information to the Code stated that unless access to promotional material about prescription only medicines was limited to health professionals and appropriate administrative staff, a pharmaceutical company website must provide information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified. This was to avoid the public needing to access material for health professionals unless they chose to.

The front page of the website in question had two clearly labelled sections; one 'For UK healthcare professionals' and the other 'For patients and public'. The section for health professionals stated that 'If you are a UK health professional and would like more information on Pradaxa ... please click here'. The next screen referred to educational packs and required a choice between the two indications. The health professional part of the site was clearly promotional. The banner at the top of each page stated, inter alia, 'For UK healthcare professionals only'.

The Panel noted that the patient and public section of the website contained a short product overview and access to the Pradaxa patient information leaflets (PILs) and summaries of product characteristics (SPCs) via a link to the electronic medicines compendium (eMC).

The Panel considered that the amount of information in the public and patient section was on the limits of acceptability in order to avoid that audience needing to access material intended for health professionals. The sections for health professionals and for patients/public were clearly separated and labelled such that the intended audience for each was clear. On balance the Panel did not consider that the open access nature of the material for health professionals meant that prescription only medicines were being advertised to the public as alleged and ruled no breach of the Code which was upheld on appeal from the complainant.

The complainant noted that the first reference to the indication of stroke prevention in atrial fibrillation did not specify that this only referred to 150/110mg doses of Pradaxa and did not include the 75mg dose. The hyperlinked content was similar. This omission was misleading and clinically relevant.

The Panel noted that the recommended dose of Pradaxa for the prevention of stroke and systemic embolism in certain patients was 150mg twice daily (110mg twice daily in patients aged 80 or over). These dose recommendations could be accessed by clicking on a 'Dose' tab. The Panel did not consider that the failure to refer to the 75mg dose in the section clearly marked 'Stroke prevention in atrial fibrillation' was misleading as alleged. No breach was ruled.

The complainant noted that the location of the prescribing information was only clarified after prominent claims for Pradaxa.

The Panel noted that the first page of the site, following confirmation that the reader was a UK health professional, referred to the licensed indications but did not indicate where the prescribing information could be found. The reader had to click on the relevant indication before reaching the page which contained a link to the prescribing information. In the Panel's view, the prescribing information should have appeared on the page that referred to the licensed indications for Pradaxa which followed confirmation of the reader as a health professional. This part of the site was promotional and thus a breach was ruled.

A general practitioner complained about the Pradaxa (dabigatran) website (Pradaxa.co.uk) created by Boehringer Ingelheim Limited.

Pradaxa was indicated for primary prevention of venous thromboembolic events in adults who had undergone elective total hip or total knee replacement surgery. It was also indicated for the prevention of stroke and systemic embolism in certain adult patients.

Boehringer Ingelheim was asked to consider Clauses 4.6, 7.2, 22.1, 22.2 and 24.1 of the Code.

1 Access to the website

COMPLAINT

The complainant questioned whether the access to the medical content for health professionals was sufficiently rigorous to restrict access only to health professionals and queried whether it should require General Medical Council (GMC) or other such

registration details, as was the case with many other pharmaceutical company websites. The complainant alleged that the arrangements were such that Boehringer Ingelheim clearly intended to facilitate the promotion of Pradaxa to the public.

RESPONSE

Boehringer Ingelheim submitted that the main purpose of the website was to provide health professionals with factual information, including access to prescribing information and the educational pack, about the use of Pradaxa in stroke prevention in atrial fibrillation (SPAF). The public part of the site also provided information for patients, including the patient information leaflet (PIL) and summary of product characteristics (SPC). The health professional and public sites could be accessed without any special permission (this was not a restricted site) but the health professional had to click once to confirm they were a health professional and then there was a pop-up which required them to reconfirm this.

The Pradaxa marketing access authorization and agreement with the Medicines and Healthcare products Regulatory Agency (MHRA) required Boehringer Ingelheim to make copies of the educational pack (ref DBG 2653) (consisting of the prescriber guide for stroke prevention in atrial fibrillation (ref DBG 2466), SPCs and Pradaxa patient alert card (ref DBG 2464)) available to all health professionals. The communication plan for the educational pack was agreed with the MHRA and included making downloadable versions available on the health professional side of the Pradaxa.co.uk website. Boehringer Ingelheim submitted that if access to the site was further restricted beyond the click to confirm health professional status that would defeat one of the most important purposes of the site – health professionals could be hindered in gaining instant access to the educational pack. Restricting access would also break the company's agreement with the MHRA.

There was information available for patients on the website and it was clear from the landing site which part of the website was for the public. The public was very clearly signposted to the appropriate part of the site. The main information on the public part of the site was the PIL and SPC. This information was provided so that patients had sufficient information easily available on the site to answer their questions and were therefore not tempted to enter the health professional part of the site (a requirement of Clause 24.1). Boehringer Ingelheim knew that medicines guides were sometimes also made available for patients on company websites. With a new anticoagulant such as Pradaxa the company considered that such a guide in a therapy area undergoing considerable change because of new medicines could easily be considered contentious, undermine the advice from the prescribing physician and PIL, and also risk being seen as disparaging to warfarin (or other new oral anticoagulants as they became available). There was however a brief clinical overview about anticoagulants in general. Possible side effects of anticoagulants were also explained with advice for what to be aware of in terms of bleeding and bruising and patients were advised to report any side effects. There was also information on the yellow card reporting scheme, Boehringer Drug Safety, advice to discuss side effects with the GP and possible support available from NHS Direct and their local pharmacist.

On the home page there was a clear button, 'For UK healthcare professionals', and another, 'For patients and the public'. When a health professional tried to enter the relevant section of the site a further pop up button asked for confirmation they were a UK health professional. There was no requirement for a GMC number on the 'For UK healthcare professionals' button because Boehringer Ingelheim intended the site to be easily accessible to health professionals other than doctors, especially pharmacists and nurses, who needed copies of the educational pack, prescribing information and SPC. There was no robust list of pharmacists and nurses available, comparable to the GMC list, to use to limit access to the site in a formal way.

The supplementary information to Clause 24.1 explained that when access to a website was not restricted there must be adequate information available for members of the public to avoid them choosing to access materials for health professionals. Boehringer Ingelheim stated that this meant that there did not automatically need to be restricted access.

There did not appear to be any universal standard in the UK relating to access to websites by health professionals. Some companies required a health professional to register or enter his/her GMC number to access a site but others did not.

Boehringer Ingelheim considered that when introducing a new anticoagulant it had a responsibility to provide health professionals with information about it so that they understood the medicine properly and were able to use it safely and appropriately in the right patient groups, with the right follow-up care, and were aware of adverse events and risks of treatment. With a great deal of unregulated information available on the Internet it was especially important that material was well referenced, balanced and non-promotional. This was Boehringer Ingelheim's intention with the website.

Boehringer Ingelheim submitted that the website was balanced and informative and complied with the Code, particularly Clause 7.2. The SPC should be the main source of information for any prescriber but the registration study (RE-LY) was also of interest and a link to a summary of the study was included in the clinical evidence section of the website. Providing a completely inclusive short summary of a major study was challenging and so at the end of the document three clearly visible hyperlinks provided access to the original publication in the New England Journal of Medicine, the article in the same journal about newly identified clinical events, and the supplementary

appendix which was just a few pages long but provided a useful summary of all of the main outcome measures in the intent to treat population. Boehringer Ingelheim hoped that by providing all of this data as easily accessible original publications it could be seen that it its intention had been to inform, not mislead.

Boehringer Ingelheim hoped that it had demonstrated that it was aware of the requirements of Code, particularly Clauses 7.2, 22.1, 22.2, and 24.1, and had complied with these requirements.

PANEL RULING

The Panel noted that the supplementary information to Clause 24.1 stated that unless access to promotional material about prescription only medicines was limited to health professionals and appropriate administrative staff, a pharmaceutical company website or a company sponsored website must provide information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified. This was to avoid the public needing to access material for health professionals unless they chose to.

The front page of the website in question had two clearly labelled sections; one entitled 'For UK healthcare professionals' and the other entitled 'For patients and public'. The section for health professionals stated that 'If you are a UK health professional and would like more information on Pradaxa…. please click here'. The next screen referred to the educational packs and required readers to choose between the stroke indication or the indication relating to hip/knee replacement surgery. The health professional part of the site was clearly promotional and included the educational pack, information on the mode of action, dosage and administration of the medicine. The banner at the top of each page stated 'For UK healthcare professionals only' and gave brief details of the stroke indication.

The Panel noted that the patient and public section of the website contained a short product overview for each indication and access to the PILs and SPCs for the product, via a link to the electronic medicines compendium (eMC).

The Panel considered that the information provided in the patient and public section of the website was limited, but nevertheless it was provided. The Panel queried whether the information in the public and patient section was sufficient to avoid the intended audience needing to access material intended for health professionals. The Panel considered that it was on the limits of acceptability in this regard. The sections for health professionals and for patients/public were clearly separated and labelled such that the intended audience for each section was clear, as set out in the supplementary information to Clause 24.1. On balance the Panel did not consider that the open access nature of the material for health professionals meant that prescription only medicines were being advertised to the public as alleged and ruled no breach of Clause 22.1. The Panel noted that there was no complaint about the content of the site merely the arrangements for accessing material intended for health professionals thus the Panel ruled no breach of Clause 22.2.

The Panel noted its rulings of no breach of the Code in relation to the arrangements for accessing the site and thus ruled no breach of Clause 24.1 in this regard.

APPEAL BY THE COMPLAINANT

The complainant appreciated the Panel's perspective with regard to its rulings of no breach of Clauses 22.1 and 22.2, but considered that these rulings should be referred to the Appeal Board. The complainant stated that it was evident that the product information was provided to the public and alleged that the relative 'insufficiency' of the information and content provided in the public section, compared with that for health professionals, was not appropriate or consistent with that required under Clause 22.2.

The consequence of this insufficiency of information was that it necessitated those members of the public who needed more information to, naturally and reasonably, refer to the associated content intended for health professionals. The unrestricted and close proximity of the hyperlink access to the health professionals' content clearly and intentionally helped facilitate this; the net effect was the promotion of Pradaxa to the public.

Although the complainant had not appealed the ruling of no breach of Clause 24.1, it appeared that the Panel's ruling in that regard was consequential to its rulings of no breach of Clauses 22.1 and 22.2. Boehringer Ingelheim was thus asked to address this point in its response to the appeal.

COMMENTS FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim noted that the first page of the Pradaxa website had clearly marked separate entry tabs for the public and for health professionals. The open access nature of the materials for health professionals was consistent with the Code. There was no current requirement for restricted access to websites intended for health professionals. The demarcation between the sites for the public and health professionals was clear and a member of the public could not access the health professional site by accident. Because Pradaxa was a new medicine with an MHRA approved educational pack it was especially important that health professionals could easily access this material in addition to the SPC, PIL and prescribing information. Restricted access would have been likely to impair easy access to these essential materials by health professionals. Open access to company websites in this way was also consistent with current UK practice in the pharmaceutical industry. The variety of different health professionals who required access to the site was also extensive and included doctors, nurses and pharmacists. Restricting access would have been very challenging if not impossible because

identification listings for other health professionals, comparable to GMC numbers for doctors, were currently not universally available or standardised.

Boehringer Ingelheim noted that the Code specified which materials should be provided as a library resource for the public. The SPC and PIL were UK-specific and provided extensive information which was sufficient for interested members of the public who wanted to read more about the medicine. Although the public assessment report (PAR) was available, Boehringer Ingelheim submitted that it was not necessary or desirable to include this as a reference because the extent of the information then provided, in this instance, could obfuscate the most important information from a patient perspective, namely the PIL. The PIL provided the European Medicines Agency (EMA) website address so an interested member of the public could access the EMA site and would be made aware that further information was available to them if required. The correct emphasis was given in the PIL and the advice to consult the general practitioner or pharmacist for further information was the best advice, particularly in this instance when there had been a recent extension to the product licence. In general other companies did not currently reference the PAR. There was no obligation to refer to the PAR, although providing it could be consistent with good clinical practice. In this instance Boehringer Ingelheim submitted that providing the PAR in addition to the PIL and SPC would have been excessive and potentially confusing.

Boehringer Ingelheim submitted that for medicines in an established class, medicines guides were sometimes made available for the public by UK companies. As Pradaxa was the first of the new anticoagulants to gain a licence for stroke prevention in atrial fibrillation, Boehringer Ingelheim did not think that a medicines guide was currently practical. It would have been very difficult to provide a medicines guide which did not detract from the PIL or SPC and avoided any additional product claims. As the product class expanded and clinical experience increased a medicines guide could be appropriate and Boehringer Ingelheim would keep this under review.

In conclusion, Boehringer Ingelheim agreed with the Panel's rulings and denied breaches of Clauses 22.1, 22.2 and 24.1.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant stated that it appeared that Boehringer Ingelheim had contrived many reasons for not having provided the necessary extent of information that would have been considered appropriately balanced and relevant to consumers; as was questioned by the Panel. Had this not occurred alongside the provision of the more detailed and promotional information aimed at health professionals then the question of balance would not have arisen or been a problem. Whilst the complainant conceded that restricting the health professional content might have been difficult for the reasons outlined it was still incumbent on the company to ensure that the consumer content was appropriately balanced and informative such that it did not effectively drive those who needed more to simply click on the conveniently and closely placed link to the health professional content.

The complainant stated that the provision of product information to consumers via the Internet must and could be better managed. It was bad enough that the ABPI had no remit over the many questionable materials, directly accessible to UK patients and consumers, that were promoted by non-UK based parent companies, such as Boehringer Ingelheim's, on its corporate website. However, the logistical arrangement exhibited in the website in question clearly demonstrated how UK based companies could 'safely' circumvent the regulations that prevented the promotion of products to consumers in the UK; the net effect of the Panel's ruling in this case was to facilitate this.

APPEAL BOARD RULING

The Appeal Board noted that the webpages for health professionals and those for patients/public were clearly separated and labelled such that the intended audience for each section was clear, in line with the supplementary information to Clause 24.1. The Appeal Board noted that the section of the website for patients and the public contained a short product overview for each indication and direct links to the Pradaxa PILs and SPCs via the eMC. Whilst there was no link to the PAR the EMA website address appeared at the end of the PIL from which readers would be able to access the Pradaxa PAR.

The Appeal Board noted that Clause 24.5 stated that 'Public assessment reports (European or UK), summaries of product characteristics, package leaflets and reference material for prescription only medicines *may* be included on the internet and be accessible by members of the public provided that they are not presented in such a way as to be promotional in nature.' (emphasis added). Thus although the Code advised that the PAR might be included it was not a requirement to do so.

In the Appeal Board's view the amount of information provided on the patient/public part of the website was not unreasonable. The Pradaxa SPCs and PILs were detailed. The PILs provided information designed specifically for the audience. The Appeal Board did not consider that either the amount or quality of the information provided was such that readers needed to look on the health professionals' section of the website for more information.

The Appeal Board did not consider that the open access nature of the material for health professionals and the amount of information provided to patients/public meant that a prescription only medicine had been advertised to the public as alleged and it upheld the Panel's rulings of no breach of Clause 22.1. It noted that the complaint was about the arrangements for accessing the site. The Appeal

Board upheld the Panel's ruling of no breach of Clause 22.2. The appeal was unsuccessful.

As the Appeal Board had ruled no breach Clauses 22.1 and 22.2 it did not need to consider the Panel's ruling of no breach of Clause 24.1.

2 Dose of Pradaxa

COMPLAINT

The complainant noted that the first reference to the indication of stroke prevention in atrial fibrillation did not specify that this only referred to 150/110mg doses of Pradaxa and did not include the 75mg dose. The same was the case for the hyperlinked content. This omission was misleading and clinically relevant.

RESPONSE

Boehringer Ingelheim noted that the complainant was concerned about the omission of the 75mg SPC. The company did not understand the basis for this complaint. Pradaxa was indicated for stroke prevention in SPAF (110mg and 150mg doses) and for prevention of venous thromboembolism after elective hip and knee replacement surgery (110mg and 75mg doses). On the SPAF section of the site there were hyperlinks to the relevant 150mg and 110mg doses. On the venous thromboembolism section of the site there were hyperlinks to the 110mg and 75mg dose. The company did not see how this could be any more clear or appropriate.

PANEL RULING

The Panel noted that the screen layout had nine tabs on the left hand side including 'Dose' and 'Educational pack'. As well as the heading that the page was intended for healthcare professionals the page was headed and subheaded with details of the stroke indication. The link to the SPC and the prescribing information appeared at the foot of the page.

The Panel noted that the recommended dose of Pradaxa for the prevention of stroke and systemic embolism in certain patients was 150mg twice daily. For patients aged 80 years or above this dose was decreased to 110mg twice daily. These dose recommendations could be accessed by clicking on the 'Dose' tab. The Panel did not consider that the failure to include a reference to the 75mg dose in the section clearly marked 'Stroke prevention in atrial fibrillation' was misleading as alleged. No breach of Clause 7.2 was ruled.

3 Location of prescribing information

COMPLAINT

The complainant noted that the location of where the prescribing information could be found was only clarified after prominent claims for Pradaxa had already appeared. This did not allow the reader to appreciate the promotional claims in relationship to the important information contained in the prescribing information.

RESPONSE

Boehringer Ingelheim submitted that the prescribing information was at the bottom of every page of the health professionals' part of the website (Clause 4.6).

As the complainant was critical of the availability of the prescribing information, Boehringer Ingelheim submitted that it had made the prescribing information even more prominent and added it additionally to the left hand tabs (white on dark blue) on the left hand side of each web page (for SPAF). The company considered that because the prescribing information had always been easy to find as a link at the bottom of each web page it had not contravened the Code but accepted that there was room for improvement and hoped that health professionals would find the change helpful.

On the first page of the site following confirmation of the identity of the reader as a UK health professional, there was a choice of the two indications, SPAF and the prevention of venous thromboembolism. There was no prescribing information on this page, although there were links to the three SPCs but this was because no product claims were made, there was only a statement of the licence for each indication. The company did not know if the complainant was stating that the prescribing information should be available on this page but that did not seem appropriate as it could cause confusion as to what doses were licensed for the two indications.

Boehringer Ingelheim submitted that the Pradaxa website was more visually attractive than some other companies' sites which supplied product information. However, the company had been careful not to make product claims. The information given related to the indication, dose, mode of action, initiation of Pradaxa, managing the anticoagulation effect, managing anticoagulation, clinical evidence, and access to the educational pack. The clinical evidence section was non-promotional and was a text document in black and white which gave a balanced account of the data from the RE-LY study which was relevant to the prescribers' understanding of the medicine. There were no marketing statements or claims. Boehringer Ingelheim considered that its report of the RE-LY study complied with Clause 7.2.

The company was very concerned to maintain high standards and welcomed any constructive criticism. It was inclined to attribute the negative remarks as having arisen from first impressions of the website. It was visually attractive; more so than some of its competitors' sites, but a pleasant visual aesthetic did not in itself constitute a breach of the Code.

As Pradaxa was an anticoagulant there was the potential for excess bleeding events, made more likely if it was not prescribed within the licence and

patients were not followed up appropriately. It was therefore imperative that the company provided health professionals with adequate, easily accessible information. The Pradaxa website helped the company to do that and allowed easy access to the educational pack, which was part of the agreed communication plan with the MHRA.

Boehringer Ingelheim emphasised that it took any allegation of a breach of the Code very seriously and although it considered that the Pradaxa website was not in breach it was concerned that the complainant had objected to some parts of it and therefore it had taken immediate action to improve clarity and quality by making the prescribing information links more prominent.

PANEL RULING

The Panel noted that Clause 4.6 required that promotional material on the Internet must contain a clear prominent statement as to where the prescribing information could be found.

The Panel noted that the first page of the site following confirmation of the identity of the reader as a UK health professional referred to the licensed indications for Pradaxa but did not indicate where the prescribing information could be found. The reader had to click on the relevant indication before reaching the page of the website that contained a link to the prescribing information. In the Panel's view, the prescribing information should have appeared on the page that referred to the licensed indications for Pradaxa which followed confirmation of the reader as a health professional. This part of the site was promotional. The Panel did not agree with Boehringer Ingelheim's submission that no product claims were made. Details of a product's indication was, in effect, a product claim. Nor did the Panel agree with Boehringer Ingelheim's submission that the provision of prescribing information on the first page would have caused confusion; a link to the relevant prescribing information could have been placed below each indication. A breach of Clause 4.6 was ruled in relation to the absence of a direct link to the prescribing information on the page in question.

Complaint received **19 October 2011**

Case completed **19 January 2012**

PHARMACIST v BOEHRINGER INGELHEIM

Promotion of Pradaxa

A pharmacist complained about stroke prevention leavepieces for Pradaxa (dabigatran) 110mg bd and 150mg bd and the conduct of a representative presenting a Pradaxa detail aid produced by Boehringer Ingelheim.

The complainant alleged that the title of the leavepieces 'Stroke Prevention' was misleading. Pradaxa was not licensed for stroke prevention but for prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with certain risk factors. The complainant submitted that although the front pages of the leavepieces further down referred to nonvalvular atrial fibrillation, this was not clear on first inspection.

The leavepieces went on to state that dabigatran was generally as well tolerated as warfarin. The complainant stated that in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, more patients discontinued treatment due to poor tolerability. Major bleeding was no more frequent between the groups assigned to warfarin, dabigatran 110mg bd or 150mg bd, however the higher risk of gastrointestinal (GI) side effects and GI bleeding (with 150mg bd) compared with warfarin brought in to question its use in those at risk of these effects. The trial only considered data for two years therefore long term safety was unclear.

The complainant had attended a nurse education meeting at which a Boehringer Ingelheim representative presented and had glossed over the GI side effects and stated that 'PPI [proton pump inhibitor] cover might be required'. The representative also did not mention the increased rate of myocardial infarctions (MIs) with high dose dabigatran.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the licensed indication was stated in full prominently on the front page of both leavepieces and positioned such that it would be read in conjunction with the main claim 'Stroke Prevention'. The full indication would be immediately obvious. Given its context the Panel did not consider that the claim 'Stroke Prevention' on the front page of either leavepiece was misleading or inconsistent with the Pradaxa summary of product characteristics (SPC) as alleged. No breaches of the Code were ruled including Clause 2.

The Panel noted that both leavepieces included the prominent claim that 'In RE-LY, Pradaxa was generally as well tolerated as warfarin'. Beneath the claim was a number of bullet points and additional information.

Data from the RE-LY study (Connolly *et al* 2009) showed that the discontinuation rates for both doses of Pradaxa were statistically significantly higher at 1 year and 2 years vs warfarin ($p<0.001$). Reasons for discontinuation showed, inter alia, that 2.7% of patients discontinued Pradaxa (110mg and 150mg) therapy due to serious adverse events vs 1.7% of patients assigned to warfarin ($p<0.001$). GI symptoms (including pain, diarrhoea and vomiting) prompted 2.2% of patients in the Pradaxa 110mg group to discontinue therapy, 2.1% of patients in the Pradaxa 150mg group and 0.6% in the warfarin group. These differences were not statistically significant. GI bleeding resulted in the discontinuation of therapy in 1%, 1.3% and 0.9% of patients taking Pradaxa 110mg, 150mg and warfarin, respectively. These differences were not statistically significant. Adverse events reported in any of the three treatment groups were comparable with the exception of dyspepsia which was reported by 11.8% of patients in the Pradaxa 110mg group, 11.3% of patients in the Pradaxa 150mg group and 5.8% of patients taking warfarin ($p<0.001$ for the comparison of either dose of Pradaxa and warfarin).

The Panel noted that discontinuation rates, rates of dyspepsia and bleeding reactions were discussed in bullet points beneath the claim at issue. These, however, were in a much smaller black font size whereas the claim at issue was separate and visually prominent in a larger, blue font.

The Panel considered that given the statistically significant differences between Pradaxa and warfarin with regard to dyspepsia and discontinuation of therapy because of serious adverse events, the prominent claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' did not reflect the balance of evidence and was misleading in that regard. Breaches of the Code were ruled in relation to each leavepiece. These rulings were appealed.

The leavepiece for Pradaxa 110mg included a page headed 'Rates of bleeding vs warfarin' beneath which was the prominent claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin'. The Panel noted that one of the bullet points below the claim stated that GI bleeding was higher with Pradaxa 110mg but not significantly so. In that regard the Panel did not consider that the claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin' reflected the evidence. The claim was misleading with regard to the incidence of GI bleeding and breaches of the Code were ruled. These rulings were appealed.

The leavepiece for Pradaxa 150mg also included a page headed 'Rates of bleeding vs warfarin'.

Beneath the heading was the prominent claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)'. One of the bullet points beneath the claim stated that GI bleeding was significantly higher with Pradaxa 150mg bd (warfarin, 1.07; Pradaxa 1.57: p=0.0008). The RE-LY study stated that there was a significantly higher rate of major GI bleeding with Pradaxa 150mg than with warfarin. The Panel thus considered that with regard to major GI bleeds the claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)' did not reflect the balance of the data. The claim was misleading in that regard. Breaches of the Code were ruled. These rulings were appealed.

The Panel did not consider that the leavepieces were misleading with regard to the length of time that data had been collected. No breach of the Code was ruled.

The Panel noted that the complainant had alleged that a representative at a meeting had glossed over GI side effects and stated that PPI cover might be required. It was also alleged that the representative did not mention the increased rate of MI with high dose Pradaxa.

The Panel noted that the detail aid used by the representative was about Pradaxa 150mg. With regard to the tolerability of Pradaxa vs warfarin and the incidence of GI symptoms the Panel noted that page 8 of the detail aid was the same as that discussed above for the Pradaxa 150mg leavepiece. The Panel thus considered that the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' was misleading as above and that its rulings of breaches of the Code also applied here. These rulings were appealed.

The Panel noted that the relevant part of the representatives' briefing document stated that the bullet points below the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' provided an overview of side-effects associated with Pradaxa 150mg bd. It was noted that the section provided practical guidance on managing dyspepsia (including reference to the permitted use of a concomitant PPI in the RE-LY study) and top line information about rates of MI.

With regard to the allegation that the representative had 'glossed over' GI side-effects the Panel noted it was difficult in such circumstances to determine precisely what had been said. The dyspepsia data appeared under a heading of 'generally as well tolerated as warfarin' but the briefing material had specifically drawn the representatives' attention to the management of dyspepsia. The SPC for Pradaxa 150mg stated that the administration of a PPI could be considered to prevent GI bleeding. Although noting its rulings above, the Panel, on balance, considered that on this narrow point the briefing material was not unreasonable. No breach of the Code was ruled.

The Panel noted its rulings on the representatives' briefing document and detail aid. There was no way of knowing exactly what the representative had said about GI side-effects and the Panel thus ruled no breach of the Code.

The Panel noted that both parties agreed that MI data had not been discussed at the meeting. The complainant had submitted that there was an increased rate of MI with high dose Pradaxa. The Panel noted, however, that the RE-LY study showed that although there was an increased annual MI rate in patients taking Pradaxa 150mg vs warfarin the difference was not statistically significant. The data from the RE-LY study regarding MI rate was included on page 8 of the detail aid and in each of the leavepieces provided to delegates. The Panel had no evidence before it to show that by not discussing the MI data the representative had given a misleading impression of the safety of Pradaxa as alleged. No breach of the Code was ruled.

The Panel noted its rulings above and considered that overall the materials at issue minimised a prescriber's concerns about the side effect profile of Pradaxa. The materials were misleading with regard to serious adverse events including major GI bleeding and also about the incidence of dyspepsia with Pradaxa. The Panel was concerned that the material had the potential to compromise patient safety. High standards had not been maintained. A breach of the Code was ruled which was appealed. With regard to Clause 2 the Panel considered that providing unbalanced and misleading information about the incidence of GI bleeding and major GI bleeds was a serious matter. The materials in question were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

The Appeal Board considered that the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' would be taken to mean that in most respects Pradaxa was as well tolerated as warfarin. In that regard readers would accept that some side-effects might occur more often with Pradaxa than warfarin (and vice versa) whereas for other side-effects there might be little difference between the medicines. The Appeal Board considered that readers would be familiar with the side-effect profile of warfarin and know that it had some problems with regard to tolerability. The Appeal Board noted the detailed information below the claim at issue, which, inter alia, referred to increased rates of discontinuation ($p<0.01$), dyspepsia ($p<0.01$) and myocardial infarction (p=ns) for Pradaxa 150mg and 110mg and considered on balance that given the context in which it appeared, the claim at issue was not misleading. The Appeal Board ruled no breaches of the Code in relation to both leavepieces. The appeals on this point were thus successful.

With regard to the Pradaxa 110mg leavepiece the Appeal Board noted that the claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin' appeared above four bullet points. Three of the four bullet points had details of the statistically significant advantages of Pradaxa 110mg compared with warfarin for 'Any bleeding

(major or minor)', 'Major bleeding' and 'Life-threatening bleeding'. The fourth bullet point stated that 'Gastrointestinal bleeding was higher with Pradaxa 110mg … but not significantly so …'. In the Appeal Board's view, the meaning of 'any' in the claim at issue, was not clear but considered that, given the additional detailed information immediately below it, on balance, the claim was not misleading. No breaches of the Code were ruled. The appeal on this point was successful.

With regard to the 150mg leavepiece the Appeal Board noted that the claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)' was followed by three bullet points which gave more detailed information. The Appeal Board noted that from the bullet points that 'Any bleeding (major or minor)' and 'Life-threatening bleeding' were statistically significantly lower with Pradaxa 150mg compared with warfarin and 'Gastrointestinal bleeding' was statistically significantly higher with Pradaxa 150mg. The Appeal Board thus considered that, given the context in which it appeared, the claim was not misleading. No breach of the Code was ruled. The appeal on this point was thus successful.

The Appeal Board noted that page 8 of the detail aid also featured the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' and in that regard it considered that its ruling above about the use of the claim in the leavepieces applied here. No breaches of the Code were ruled. The appeal on this point was thus successful.

The Appeal Board noted its rulings above and consequently ruled no breach of the Code was ruled including Clause 2. The appeal on this point was thus successful.

A pharmacist complained about stroke prevention leavepieces for Pradaxa (dabigatran) 110mg bd and 150mg bd and the conduct of a representative presenting the information contained within the Pradaxa detail aid. Pradaxa was marketed by Boehringer Ingelheim for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation and one or more stated risk factors.

COMPLAINT

The complainant alleged that the title of the leavepieces 'Stroke Prevention' was misleading. Pradaxa was not licensed for stroke prevention but for prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke, transient ischemic attack, or systemic embolism (SEE)
- Left ventricular ejection fraction < 40 %
- Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
- Age ≥ 75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

The complainant submitted that although the leavepieces further down referred to nonvalvular atrial fibrillation, this was not clear on first inspection. The leavepieces went on to state that dabigatran was generally as well tolerated as warfarin. The complainant stated that in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, more patients discontinued treatment due to poor tolerability. Major bleeding was no more frequent between the groups assigned to warfarin, dabigatran 110mg bd or 150mg bd, however the higher risk of gastrointestinal (GI) side effects and GI bleeding (with 150mg bd) compared with warfarin brought in to question its use in people who were at risk of these effects. The complainant submitted that the trial only considered data for two years therefore long term safety was unclear.

The complainant had attended a nurse education meeting in October, at which a Boehringer Ingelheim representative presented and had glossed over the GI side effects and stated that 'PPI [proton pump inhibitor] cover might be required'. The representative also did not mention the increased rate of myocardial infarctions (MIs) with high dose dabigatran.

When writing to Boehringer Ingelheim, the Authority asked it to consider the requirements of Clauses 3.2, 7.2, 7.9, 15.2, 15.9, 9.1 and 2 of the Code.

RESPONSE

Boehringer Ingelheim submitted that the lunchtime meeting in question was a legitimate meeting held in NHS premises organised by the GP surgery. This type of meeting gave representatives an opportunity to present product information to health professionals. The meeting was attended by five practice nurses. The representative used the certified sales aid for Pradaxa (ref DBG 2764) and attendees were also given the two leavepieces at issue and a Pradaxa educational pack (DBG 2653) (copies of all materials were provided). The marketing authorization for Pradaxa and agreement with the Medicines and Healthcare products Regulatory Agency (MHRA) required Boehringer Ingelheim to make copies of the Pradaxa educational pack available to all potential prescribers. The pack consisted of the prescriber guide (DBG 2466), summaries of product characteristics (SPCs) for Pradaxa 110mg (DBG 2687) and Pradaxa 150mg (DBG 2637) and a patient alert card (DBG 2464). The pack was also offered to other health professionals (eg nurses, pharmacists, etc). Boehringer Ingelheim noted that all of the materials used at the meeting had been pre-vetted by the MHRA. There was no formal agenda for the meeting; however, as mentioned above, there was a discussion using the Pradaxa detail aid.

Boehringer Ingelheim submitted that the title 'Stroke Prevention', which appeared on the first page of the

detail aid and leavepieces, included the full licensed indication for Pradaxa positioned directly underneath it. Boehringer Ingelheim therefore considered that the title could not be read in isolation nor could it be unclear (as the complainant alleged) since the full licensed indication could not be ignored or missed and hence it refuted the allegation that the title was misleading.

With regard to the comparative tolerability of Pradaxa vs warfarin, Boehringer Ingelheim submitted that the claim in the leavepiece, 'In RE-LY Pradaxa was generally as well tolerated as warfarin' was based upon the fact that the rate of adverse events was similar across the three treatment arms in RE-LY (Pradaxa 110mg bd, Pradaxa 150mg bd and warfarin) except for dyspepsia and GI bleeding (where rates were higher with Pradaxa). 'Any bleeding' was significantly lower with Pradaxa 150mg bd and 110mg bd compared with warfarin. Discontinuation rates in RE-LY were significantly more common for Pradaxa but the most common cause for this was 'patient decision' rather than 'poor tolerability'. Boehringer Ingelheim therefore considered that the above claim could be substantiated and that it fairly reflected the evidence. A copy of the RE-LY trial was provided.

Boehringer Ingelheim disagreed with the complainant's statement that 'major bleeding was no more frequent between the groups assigned to warfarin, dabigatran 110mg bd or 150mg bd however the higher risk of GI side effects and GI bleeding (with 150mg bd) compared with warfarin brought into question its use in people who were at risk of these effects.' In the RE-LY study, compared with warfarin, Pradaxa 150mg had similar rates of major bleeding (primary safety outcome end-point) while Pradaxa 110mg had significantly lower rates.

Boehringer Ingelheim stated that the leavepieces clearly mentioned the higher rates of GI bleeding with Pradaxa compared with warfarin. The leavepieces also clearly mentioned, as per the licensed indication and SPC, that Pradaxa 150mg bd was the recommended dose for stroke prevention in atrial fibrillation and that 110mg bd was the appropriate dose (for stroke prevention in atrial fibrillation) for patients over 80 years or taking concomitant verapamil. In certain situations (eg where thromboembolic risk was low and bleeding risk was high) a patient might need to be changed over to, or initiated on, Pradaxa 110mg bd. The leavepieces clearly stated that Pradaxa 110mg bd could also be considered for patients with gastritis, esophagitis or gastroesophageal reflux, active ulcerative GI disease or recent GI bleeding. Boehringer Ingelheim therefore considered that the presentation of the data for the use of Pradaxa in patients at high risk of bleeding was entirely appropriate.

Boehringer Ingelheim was unclear to what the complainant was referring when she stated that 'The trial only considered data for two years therefore long term safety was unclear'. There were no claims in the leavepiece about the long term safety of Pradaxa. The leavepiece only referred to the RE-LY trial upon which the licensed indication of Pradaxa was based.

With regard to what the representative said about Pradaxa, Boehringer Ingelheim submitted that within the leavepiece there was a clear and appropriate mention of the GI side effects of the medicine. It also clearly stated there was higher incidence of dyspepsia and GI bleeding with Pradaxa. In addition information on concomitant PPI use with Pradaxa, as referenced from the RE-LY trial and the SPC, was also highlighted. Boehringer Ingelheim noted that the SPC stated in Section 4.4, under haemorrhagic risk that, 'The administration of a PPI can be considered to prevent GI bleeding'. The representative had confirmed that the GI bleeding data was discussed at the meeting and in that regard her conduct was entirely appropriate.

The representative in question had confirmed that MI data was not specifically discussed at the meeting. However, although the MI rate was numerically higher with Pradaxa compared with warfarin, the increase was not significant. Boehringer Ingelheim considered that the presentation of the data on MI from the RE-LY study within the leavepieces was clear, fair and balanced, substantiated and entirely appropriate. The representative also confirmed that overall it was a very comprehensive discussion and only the certified materials were used in the meeting.

Boehringer Ingelheim stated that the representative in question had passed the ABPI Medical Representatives Exam (a copy of the certificate was provided) and had been comprehensively trained on Pradaxa and had passed a compulsory, internally validated, certified training examination on the disease area, the product and all the SPCs. This training course also included training on the use of the certified promotional materials. Boehringer Ingelheim submitted that all representatives had had to pass this examination before they were allowed to promote Pradaxa.

The representative has been with Boehringer Ingelheim for five years and three months and had always maintained high standards of professional conduct. She won the annual Boehringer Ingelheim Specialist Representative of the Year award for 2010 at the 2011 annual sales conference.

Boehringer Ingelheim stated that, as highlighted above, the Pradaxa detail aid and leavepieces and the meeting, only promoted Pradaxa in accordance with its marketing authorization. It considered that all the promotional pieces used at the meeting complied with Clause 3.2.

Boehringer Ingelheim considered that the above demonstrated that the information and claims within the detail aid and leavepieces were accurate, balanced, fair, objective and unambiguous and that these materials and the meeting itself complied with Clause 7.2. Information and claims made about side effects within the detail aid and leavepieces and the meeting reflected the available evidence and Boehringer Ingelheim considered that these materials and the meeting complied with Clause 7.9.

Boehringer Ingelheim considered that it had demonstrated above that the representative appropriately presented the certified promotional material at a legitimate meeting for health professionals. The representative maintained high standards of ethical conduct in the discharge of her duties and complied with all relevant requirements of the Code including Clause 15.2. The only material used by the representative was certified promotional material. This included an associated certified brief for how to use the material (a copy was provided). The company considered that it had complied with Clause 15.9.

Boehringer Ingelheim submitted that the meeting and promotional material used were entirely appropriate and compliant with the Code. It considered that it had maintained high standards and therefore had complied with Clause 9.1. Given the above, Boehringer Ingelheim considered that it had not brought discredit to, or reduced confidence in, the pharmaceutical industry and hence had complied with Clause 2.

PANEL RULING

The Panel noted that the leavepieces for Pradaxa 150mg and 110mg were closely similar. Each bore, on the front page, an outline lateral image of a brain: on the front half of the brain was an image of a lightening storm, on the back half was an image of an older couple riding bicycles. Superimposed in bold across the brain was the claim at issue 'Stroke Prevention'. The licensed indication appeared in full on the right hand side of the page immediately beneath the image of the brain beginning about half way down the front page. The bottom right hand corner featured the product name above the claim 'Stroke prevention in atrial fibrillation'. A red banner 'Pradaxa 110mg bd – Effective stroke reduction versus warfarin in eligible patients with an increased risk of bleeding' ran along the top of the 110mg dose leavepiece. The equivalent banner at the top of the 150mg bd leavepiece read 'Pradaxa 150mg bd – More effective stroke prevention versus warfarin in eligible patients with atrial fibrillation'. A highlighted blue triangle in the top left hand corner of each leaflet read 'New 110mg b.d.' and 'New 150mg b.d.' respectively.

The Panel noted that the licensed indication was stated in full prominently on the front page of both leavepieces and positioned such that it would be read in conjunction with the main claim 'Stroke Prevention'. Its prominence was assisted by the use of black font on a white background. The Panel considered that the full indication would be immediately obvious to readers. Given the context in which it appeared the Panel did not consider that the claim 'Stroke Prevention' on the front page of either leavepiece was misleading or inconsistent with the particulars listed in the Pradaxa SPCs as alleged. No breach of Clauses 7.2 and 3.2 was ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2.

The Panel noted that both leavepieces included the prominent claim that 'In RE-LY, Pradaxa was generally as well tolerated as warfarin'. Beneath the claim was a number of bullet points and additional information.

Data from the RE-LY study (Connolly *et al* 2009) showed that the discontinuation rates for both doses of Pradaxa were statistically significantly higher at 1 year and 2 years vs warfarin ($p<0.001$). Reasons for discontinuation showed, *inter alia*, that 2.7% of patients discontinued Pradaxa (110mg and 150mg) therapy due to serious adverse events vs 1.7% of patients assigned to warfarin ($p<0.001$). GI symptoms (including pain, diarrhoea and vomiting) prompted 2.2% of patients in the Pradaxa 110mg group to discontinue therapy, 2.1% of patients in the Pradaxa 150mg group and 0.6% in the warfarin group. These differences were not statistically significant. GI bleeding resulted in the discontinuation of therapy in 1%, 1.3% and 0.9% of patients taking Pradaxa 110mg, 150mg and warfarin respectively. These differences were not statistically significant. With regard to adverse events which were reported in more than 5% of patients in any of the three treatment groups, the percentage of patients reporting each event was comparable across the groups with the exception of dyspepsia (defined to include upper abdominal pain, abdominal pain/discomfort and dyspepsia) which was reported by 11.8% of patients in the Pradaxa 110mg group, 11.3% of patients in the Pradaxa 150mg group and 5.8% of patients taking warfarin ($p<0.001$ for the comparison of either dose of Pradaxa and warfarin).

The Panel noted that discontinuation rates, rates of dyspepsia and bleeding reactions were discussed in bullet points beneath the claim at issue. These, however, were in a much smaller black font size whereas the claim at issue was separate and visually prominent in a larger, blue font. The Panel noted that it was a principle under the Code that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like. The Panel thus did not consider that the claim at issue could take the benefit of the bullet points below.

The Panel considered that given the statistically significant differences between Pradaxa and warfarin with regard to dyspepsia and discontinuation of therapy because of serious adverse events, the prominent claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' did not reflect the balance of evidence and was misleading in that regard. A breach of Clauses 7.2 and 7.9 was ruled in relation to each leavepiece. These rulings were appealed.

The Panel noted that the leavepieces for Pradaxa 110mg and 150mg differed with regard to the data included about bleeding rates and so it considered each piece separately.

The leavepiece for Pradaxa 110mg included a page headed 'Rates of bleeding vs warfarin'. Beneath the heading was the prominent claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin'. Although there were a number of bullet points beneath the claim, the Panel again

noted that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like.

The Panel noted that one of the bullet points below the claim stated that GI bleeding was higher with Pradaxa 110mg but not significantly so. In that regard the Panel did not consider that the claim 'Significantly lower rates of *any*, major and life-threatening bleeding vs warfarin' (emphasis added) reflected the evidence. The claim was misleading with regard to the incidence of GI bleeding with Pradaxa 110mg vs warfarin. A breach of Clauses 7.2 and 7.9 was ruled. These rulings were appealed.

The leavepiece for Pradaxa 150mg also included a page headed 'Rates of bleeding vs warfarin'. Beneath the heading was the prominent claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)'. One of the bullet points beneath the claim stated that GI bleeding was significantly higher with Pradaxa 150mg bd (warfarin, 1.07; Pradaxa 1.57: p=0.0008). The RE-LY study stated that there was a significantly higher rate of major GI bleeding with Pradaxa 150mg than with warfarin. The Panel thus considered that with regard to major GI bleeds the claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)' did not reflect the balance of the data. The claim was misleading in that regard. A breach of Clauses 7.2 and 7.9 was ruled. These rulings were appealed.

The Panel noted the complainant's concern that the RE-LY study had only considered data for two years and so the long term safety was unclear. In the Panel's view neither leavepiece implied that the data presented was from a long term study. An explanation of the RE-LY study stated that patients had been followed for a median of 2 years. The Panel did not consider that the leavepieces were misleading with regard to the length of time that data had been collected. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant had alleged that a representative at a meeting had glossed over GI side effects and stated that PPI cover might be required. It was also alleged that the representative did not mention the increased rate of MI with high dose Pradaxa.

The Panel noted that, in addition to the provision of the leavepieces discussed above, the representative had used the detail aid at the meeting in question. The detail aid (ref DBG 2764) was about Pradaxa 150mg. With regard to the tolerability of Pradaxa vs warfarin and the incidence of GI symptoms the Panel noted that page 8 of the detail aid was the same as that discussed above for the Pradaxa 150mg leavepiece. Thus although it was stated that rates of dyspepsia were significantly higher for Pradaxa than for warfarin (p<0.001) and that more Pradaxa patients discontinued therapy as a result of GI symptoms, this data appeared below the prominent claim 'In RE-LY Pradaxa was generally as well tolerated as warfarin'. The Panel thus considered that the claim was misleading as above and that its ruling of a breach of Clauses 7.2 and 7.9 also applied here. These rulings were appealed as above.

The Panel noted that the representatives' briefing document for page 8 of the detail aid stated that the bullet points below the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' provided an overview of side-effects associated with Pradaxa 150mg bd. It was noted that the section provided practical guidance on managing dyspepsia (including reference to the permitted use of a concomitant PPI in the RE-LY study) and top line information about rates of MI.

The Panel noted the complainant's allegation that the representative had 'glossed over' GI side-effects. It was difficult in such circumstances to determine precisely what had been said. The dyspepsia data appeared under a heading of 'generally as well tolerated as warfarin' but the briefing material had specifically drawn the representatives' attention to the management of dyspepsia. The SPC for Pradaxa 150mg stated that the administration of a PPI could be considered to prevent GI bleeding. Although noting its rulings above, the Panel, on balance, considered that on this narrow point the briefing material was not unreasonable. No breach of Clause 15.9 was ruled.

The Panel noted its rulings above on the representatives' briefing document and detail aid. There was no way of knowing exactly what the representative had said about GI side-effects and the Panel thus ruled no breach of Clause 15.2.

The Panel noted that both parties agreed that MI data had not been discussed at the meeting. The complainant had submitted that there was an increased rate of MI with high dose Pradaxa. The Panel noted, however, that the RE-LY study, upon which the material at issue was largely based, showed that although there was an increased annual MI rate in patients taking Pradaxa 150mg vs warfarin (0.81% vs 0.64%) the difference was not statistically significant. The data from the RE-LY study regarding MI rate was included on page 8 of the detail aid and in each of the leavepieces provided to delegates. The Panel did not consider that it was necessary for representatives always to refer to all of the data given in a detail aid providing that what they did say about a medicine was not misleading or ambiguous by commission or omission. The Panel had no evidence before it to show that by not discussing the MI data the representative had given a misleading impression of the safety of Pradaxa as alleged. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above and considered that overall the promotional materials at issue minimised a prescriber's concerns about the side effect profile of Pradaxa. The materials were misleading with regard to serious adverse events including major GI bleeding and also about the incidence of dyspepsia with Pradaxa. The Panel was concerned that the material had the potential to compromise patient safety. High standards had not been maintained. A breach of Clause 9.1 was ruled

which was appealed. With regard to Clause 2, which was used as a sign of particular censure, the Panel considered that providing unbalanced and misleading information about the incidence of GI bleeding and major GI bleeds was a serious matter. The materials in question were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

APPEAL BY BOEHRINGER INGELHEIM

Boehringer Ingelheim noted that the materials at issue were pre-vetted and approved by the MHRA which should be considered when assessing whether they were a true representation of the data from the RE-LY study, the registration study for the extension of the product licence. Part of the function of the MHRA's pre-vetting was to ensure that the materials were factually accurate and not likely to mislead. This was especially pertinent when considering whether the materials were of a high standard (Clause 9.1) and likely to bring the industry into disrepute (Clause 2). Boehringer Ingelheim submitted that all the materials were of a high standard and their approval by the MHRA supported this.

Boehringer Ingelheim appreciated that it was very important to disclose all relevant data relating to the use of a new medicine and submitted that its materials drew attention to dyspepsia, discontinuation data and GI bleeding in a prominent way. As this data was not favourable towards Pradaxa, Boehringer Ingelheim submitted that it had been particularly open and displayed this data prominently in its materials so that prescribers were given the relevant facts to make the best decision for their patients and relate the data to their patients' individual risk: benefit profile. This did not detract from the positive data for Pradaxa, in particular reduction in the primary efficacy endpoint of the study, stroke and systemic embolism, and the primary safety endpoint, major haemorrhage, which consisted of the composite of life threatening, non life-threatening and GI bleeding (clearly defined within the RE-LY study).

Boehringer Ingelheim noted that both leavepieces (110mg and 150mg dosages) included the claim 'In RE-LY Pradaxa was generally as well tolerated as warfarin'. Table 4 in the RE-LY study summarised discontinuations, adverse events, and liver function test results. Comparing the results for either dose of Pradaxa and warfarin, a clear pattern emerged; discontinuations were higher in the Pradaxa groups than the warfarin groups, as was dyspepsia. All other comparisons between warfarin and Pradaxa were similar. The authors noted that 'The only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia.' The RE-LY trial was not double-blind and this might have affected the discontinuation rate in the Pradaxa arms of the study, patients were more likely to be concerned by symptoms arising from the use of a new medicine (Pradaxa was not fully assessed for the new indication of stroke prevention in atrial fibrillation at that time) than an established one such as warfarin. The claim only stated that, in general, tolerability was as good as warfarin. It was therefore not incorrect. The bullet points provided further explanation to the claim by providing data on dyspepsia and discontinuation in RE-LY. Boehringer Ingelheim did not agree that the rulings of breaches of Clauses 7.2, 7.9 and especially Clauses 9.1 and 2 were appropriate when it had adopted such an open approach to sharing this data. This data was not hidden in a footnote and, although slightly smaller font was used than that in the blue sub-heading, it was prominently displayed and was immediately apparent to the reader.

Boehringer Ingelheim submitted that the aim in these materials was to clearly communicate the data from RE-LY. Boehringer Ingelheim knew it needed to prioritise safety and share clinical trial data with prescribers which was why it had claimed that Pradaxa was as well tolerated as warfarin but then listed more detailed relevant data underneath. Boehringer Ingelheim should not be penalised for being open with the data. The issue here was the heading, 'In RE-LY Pradaxa was generally as well tolerated as warfarin'. The use of the word 'tolerated' here warranted further consideration. This would be understood to be synonymous with overall safety. Major haemorrhage was the primary safety outcome of the RE-LY study and the 150mg dose of Pradaxa was associated with a similar rate of major haemorrhage to warfarin. Table 4 in Section 4.8 of the Pradaxa 150mg SPC referred to bleeding events broken down to major and any bleeding in this pivotal study. For these reasons, and because the dyspepsia rate was prominently displayed with appropriate statistical detail and referencing, it did not constitute a breach of Clauses 7.2 and 7.9.

Boehringer Ingelheim noted that the second point noted by the Panel related to the presentation of bleeding data for Pradaxa 110mg. There was omission of the gastrointestinal rates of bleeding in the heading but this data was displayed prominently underneath in the bullet points. Whilst it was understood that it was not acceptable to hide unfavourable data by the use of footnotes, this piece did not hide the data in any way, it was prominently displayed and would not be missed by the reader. Boehringer Ingelheim noted (table 5 in the Pradaxa 110mg SPC) that GI bleeding was a sub-category of major bleeding. Therefore one approach to displaying this data would have been to omit reference to GI bleeding altogether, Boehringer Ingelheim did not do this because it believed it was important that prescribers were aware of this data so they could better decide which anticoagulant would be the better choice for their patient. Definitions of the different types of bleeding were also given which was helpful for a complete understanding of the data. The Panel's ruling highlighted the word 'any' in the claim, 'Significantly lower rates of any, major and life threatening bleeding vs warfarin'. If the claim had been for significantly lower rates of 'all' bleeding (meaning all types or categories of bleeding) this would have been misleading but the word 'any' was not in breach. 'Any' referred to the sum of all bleeding. Table 5 in Section 4.8 of the SPC for

Pradaxa 110mg also included this data. In table 3 of the addendum to the RE-LY study the main categories of bleeding used in RE-LY were given which should also be considered. For all categories of bleeding the data were either the same or statistically better for Pradaxa 110mg than warfarin: the primary safety outcome of major haemorrhage was better than warfarin as was minor bleeding, major or minor bleeding, and intra-cranial bleeding; extracranial bleeding was not statistically different to warfarin. The subcategories of major bleeding were statistically better than warfarin (life threatening bleeding) or not statistically different from warfarin bleeding (non-life-threatening bleeding or gastrointestinal bleeding). Boehringer Ingelheim noted that there were many different categories of bleeding. The data for Pradaxa 110mg vs warfarin and GI bleeding was given in the leavepiece even though there was no statistical difference between the two. The relative risk of GI bleeding for Pradaxa 110mg vs warfarin was 1.08 (CI 0.85-1.38), p=0.52 (table 3, addendum). There was an 8% increase in GI bleeding with Pradaxa 110mg vs warfarin which was not statistically significant. This data was very clearly displayed. It was not usual practice to include all non-statistical results in promotional items in this way but Boehringer Ingelheim had a policy of disclosing all relevant data for prescribers and it submitted that this representation of the data reflected good practice and transparency and was not in breach of Clauses 7.2 and 7.9.

Boehringer Ingelheim noted that the third point noted by the Panel related to the leavepiece for Pradaxa 150mg and rates of bleeding. In this instance the heading was neutral, 'Rates of bleeding vs warfarin', no claim was made. The sub-heading in blue read, 'Similar rates of major bleeding vs warfarin (primary safety outcome)'. This claim could not be disputed; it was the primary safety outcome and could not be considered to be in any way misleading. In plain text bullet points underneath this sub-heading the data for any bleeding (major and minor), life threatening bleeding and gastrointestinal bleeding was given. Boehringer Ingelheim did not understand how the Panel could rule this in breach of Clauses 7.2 and 7.9. If the GI bleeding data had been omitted that would have been misleading. GI bleeding was a secondary safety outcome, albeit an important one. The sub-heading gave the primary safety outcome and other important secondary safety outcomes were listed in the bullet points, this was completely appropriate. The data regarding GI bleeding was prominently displayed and immediately obvious to the reader. It was not hidden as a footnote, there was not much text on this page, it could not be missed when looking through the leavepiece and this was Boehringer Ingelheim's intention, to accurately inform the prescriber about Pradaxa 150mg bleeding data. The balance of the data was accurately displayed and Boehringer Ingelheim strongly refuted any breach of Clauses 7.2 and 7.9.

Boehringer Ingelheim noted that the fourth area of concern expressed by the Panel was about dyspepsia in the detail aid (page 8). The Panel considered that the heading, 'In RE-LY Pradaxa was generally as well tolerated as warfarin' was misleading. Boehringer Ingelheim submitted that this was not the case because with the exception of dyspepsia, as explained above, Pradaxa 150mg was as well tolerated as warfarin. The term 'in general' meant exactly that, it did not mean tolerance of Pradaxa 150mg and warfarin were identical. In order to clarify this, the bullet points underneath addressed dyspepsia in some detail. The statement regarding tolerance was accurate in general. Because this was expanded upon for clarity, and referenced appropriately, Boehringer Ingelheim strongly refuted that this was in breach of Clauses 7.2 and 7.9 as alleged. The data regarding dyspepsia in the detail aid was extensive and detailed. Discontinuation rates were documented in addition to dyspepsia and the discontinuation rates for dyspepsia were also provided. This level of detail regarding dyspepsia demonstrated Boehringer Ingelheim's commitment to accurately communicate relevant clinical data to prescribers. The emphasis here was as much on communication of the data and education regarding Pradaxa as it was promotional. The ruling of breaches of Clauses 7.2 and 7.9 was not justified. Furthermore, Boehringer Ingelheim also provided the same advice regarding how to manage dyspepsia as used by the clinicians in the RE-LY study. This did not 'gloss over' the issue but disclosed relevant data and shared with prescribers the practical approach taken in the RE-LY study by many investigators.

Boehringer Ingelheim noted that the Panel had expressed concern about the information given on major bleeding, GI bleeding and dyspepsia and had ruled breaches of Clauses 9.1 and 2. Boehringer Ingelheim did not understand how this could be justified. Boehringer Ingelheim submitted that it had been transparent with the data and had presented any unfavourable data in detail for the benefit of the prescriber; no aspect of the data relating to bleeding or dyspepsia had been withheld or glossed over. The entire tone of the material was to promote safe and appropriate prescribing. The use of headings and sub-headings was not misleading and therefore not in breach of Clauses 7.2 and 7.9, and equally the openness and full and balanced account of the data did not justify a ruling that Boehringer Ingelheim had not maintained high standards or brought the industry into disrepute. Boehringer Ingelheim accepted that it must maintain neutral headings and not overclaim and would continue to prioritise this, so it welcomed this complaint as a means of further improving the quality of its materials, but denied breaches of Clauses 7.2, 7.9, 9.1 and 2.

COMMENTS FROM THE COMPLAINANT

The complainant noted that in a 2 year follow-up, the RE-LY study demonstrated that the lower dose of Pradaxa was non-inferior to warfarin at reducing the risk of stroke and systemic embolism in patients with atrial fibrillation.

The complainant noted that the mean rates for major bleeding were 2.71% per year for low dose Pradaxa,

3.11% per year for high dose Pradaxa and 3.36% for warfarin. Low dose Pradaxa was associated with a reduced risk of major bleeding; more patients discontinued Pradaxa than warfarin during the study – was this poor tolerability? However, the patients and doctors were aware of the treatment (Pradaxa or warfarin) therefore this might have affected the perception of side effects. There was no significant difference between the high dose Pradaxa and warfarin.

The complainant alleged that the leaflets were misleading in the light of the evidence.

The leaflet included the discontinuation due to GI symptoms below the claim that '… Pradaxa was generally as well tolerated as warfarin' and the complainant alleged this to be misleading.

The complainant alleged that with regard to monitoring, current warfarin services were a fixed cost due to existing infrastructure, therefore it seemed unlikely that there would be any real cost savings associated with the development of warfarin alternatives. For patients at high risk of stroke, warfarin was recommended although aspirin could be considered where warfarin was contraindicated. For moderate risk either warfarin or aspirin could be considered and for low risk aspirin was recommended. Potential bleeding risk must be considered in all cases where long-term anticoagulation was indicated. Plavix (clopidogrel) was not licensed for stroke prevention in patients with atrial fibrillation.

The complainant stated that in the RE-LY study serious adverse events leading to the discontinuation of Pradaxa occurred more frequently with both doses of Pradaxa (2.7%) than with warfarin (1.7%: p<0.001: number needed to harm (NNH) 100). Dyspepsia occurred in 5.8% patients on warfarin, 11.8% on 110mg Pradaxa and 11.3% 150mg Pradaxa.

APPEAL BOARD RULING

The Appeal Board noted Boehringer Ingelheim's submission that its material had been pre-vetted and approved by the MHRA. In that regard, however, the Appeal Board noted that the Code extended beyond the relevant UK legal requirements and that it and the Panel had to consider the material in the context of a complaint. Pre-vetting by the MHRA did not preclude rulings of breaches of the Code.

The Appeal Board noted that the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' appeared in both leavepieces above a number of bullet points and additional information. The Appeal Board considered that the claim would be taken to mean that in most respects Pradaxa was as well tolerated as warfarin. In that regard readers would accept that some side-effects might occur more often with Pradaxa than warfarin (and vice versa) whereas for other side-effects there might be little difference between the medicines. The Appeal Board considered that readers would be familiar with the side-effect profile of warfarin and know that it had some problems with regard to tolerability. The Appeal Board noted the detailed information below the claim at issue, which, inter alia, referred to increased rates of discontinuation (p<0.01), dyspepsia (p<0.01) and myocardial infarction (p=ns) for Pradaxa 150mg and 110mg and considered on balance that given the context in which it appeared, the claim at issue was not misleading. The Appeal Board ruled no breach of Clauses 7.2 and 7.9 in relation to both leavepieces. The appeals on this point were thus successful.

With regard to the Pradaxa 110mg leavepiece the Appeal Board noted that the claim 'Significantly lower rates of any, major and life-threatening bleeding vs warfarin' appeared above four bullet points which gave more detailed information taken from a number of sources including the SPC. Three of the four bullet points had details of the statistically significant advantages of Pradaxa 110mg compared with warfarin for 'Any bleeding (major or minor)', 'Major bleeding' and 'Life-threatening bleeding'. The fourth bullet point stated that 'Gastrointestinal bleeding was higher with Pradaxa 110mg … but not significantly so …'. The Appeal Board was concerned that there was a difference between the ordinary use of the word 'any' and 'any' as used in the Pradaxa 110mg SPC. The Panel had taken 'any' to mean 'all' whereas 'any' in table 5 of the SPC referred to major (intracranial, GI and fatal) bleeding plus minor bleeding. In the Appeal Board's view, the meaning of 'any' in the claim at issue, was not clear but considered that, given the additional detailed information immediately below it, on balance, the claim was not misleading. No breach of Clauses 7.2 and 7.9 was ruled. The appeal on this point was successful.

With regard to the 150mg leavepiece the Appeal Board noted that the claim 'Similar rates of major bleeding vs warfarin (primary safety outcome)' was followed by three bullet points which gave more detailed information. The Appeal Board noted that from the bullet points that 'Any bleeding (major or minor)' and 'Life-threatening bleeding' were statistically significantly lower with Pradaxa 150mg compared with warfarin and 'Gastrointestinal bleeding' was statistically significantly higher with Pradaxa 150mg. The Appeal Board thus considered that, given the context in which it appeared, the claim was not misleading. No breach of Clauses 7.2 and 7.9 was ruled. The appeal on this point was thus successful.

The Appeal Board noted that page 8 of the detail aid also featured the claim 'In RE-LY, Pradaxa was generally as well tolerated as warfarin' and in that regard it considered that its ruling above about the use of the claim in the leavepieces applied here. No breach of Clauses 7.2 and 7.9 was ruled. The appeal on this point was thus successful.

The Appeal Board noted its rulings above and consequently ruled no breach of Clauses 9.1 and 2. The appeal on this point was thus successful.

Complaint received **28 October 2011**

Case completed **23 February 2012**

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM and LILLY

Promotion of Trajenta

A general practitioner complained about a Trajenta (linagliptin) leavepiece entitled 'Control and care matter'. Trajenta was co-marketed by Boehringer Ingelheim and Lilly for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults. It could be used as monotherapy or combination therapy.

The complainant alleged that the campaign to sell Trajenta as a DPP-4 [dipeptidyl peptidase 4] inhibitor that was 'different' from others in the class relied on misleading, unbalanced/selective, unsubstantiable and grossly exaggerated/distorted material. The complainant noted that the headline across pages 2 and 3 of the leavepiece was 'Glycaemic control … with a difference …'. Page 3 featured a list of various differences which were wholly or partially incorrect with reference to the headline which invited a direct comparison with the other DPP-4 inhibitors referred to in the leavepiece.

The complainant submitted that, compared with saxagliptin the only valid differences were that: Trajenta was the first DPP-4 inhibitor primarily excreted via the bile; that 5% of the Trajenta dose was excreted via the kidney and that no dosage adjustment was required for patients with hepatic impairment.

The complainant alleged that in the management of type 2 diabetics with renal impairment, Trajenta was not different or the first DPP-4 inhibitor, as implied; saxagliptin could also be used with no dose adjustment in mild renal impairment. Trajenta could only claim to be different from saxagliptin with regard to its use specifically in patients with moderate and severe renal impairment where no dose adjustment was necessary; to suggest saxagliptin could never be used without dosage adjustment was misleading, exaggerated and endangered patient safety.

The claim that no additional treatment-related renal monitoring was required with Trajenta was alleged to be misleading and potentially dangerous. This might be the case when Trajenta was used as a monotherapy but not so when used in combination with metformin, in this regard the National Institute for Health and Clinical Excellence (NICE) guidelines advocated regular renal monitoring of patients with type 2 diabetes as a required aspect of good clinical practice; to suggest otherwise for the use of Trajenta (even in monotherapy) was irresponsible.

The leavepiece suggested that Trajenta was appropriate in adult patients with type 2 diabetes at high risk of declining renal function. The complainant questioned how this squared with the claim that such patients could be managed with Trajenta without the need for additional treatment-related renal monitoring. The placement of the claim that Trajenta was appropriate in adult patients with type 2 diabetes at high risk of declining renal function, under the banner of glycaemic control with a difference, also suggested that Trajenta was different to the other DPP-4 inhibitors; this was not so as all DPP-4 inhibitors could be used to treat these patients.

The headline 'Glycaemic control … with a difference …' also suggested that Trajenta had been specifically licensed for indications that were somehow different from the other DPP-4 inhibitors.

The complainant alleged that the way in which the above information was laid out under the banner of 'Glycaemic control … with a difference…', suggested that the glycaemic control offered by Trajenta (ie reductions in HbA_{1c} vs placebo) was somehow directly, solely and causally related to the mode of excretion in bile, no requirement to adjust dosages or renal/hepatic monitoring; this could not be substantiated.

The complainant submitted that the leavepiece also stated that Trajenta was different from the other DPP-4 inhibitors in that it was the first one dose, once daily DPP-4 inhibitor excreted primarily via the bile: no dose adjustment required. This claim was general, all encompassing and misleading given that saxagliptin was also a once-daily medicine which did not require dose adjustment in mild renal impairment. Trajenta was also not different with regard to the implied claim that it only could be taken with or without food.

The complainant stated that as there were no published, randomized, controlled trials comparing the safety and efficacy of Trajenta with sitagliptin, vildagliptin and saxagliptin the claim 'Glycaemic control… with a difference…' could not be substantiated. It appeared that the emphasis of the leavepiece was to specifically compare only those aspects of the summaries of product characteristics (SPCs) relating to dosing requirements according to renal impairment, but even this had been deliberately misrepresented with respect to saxagliptin and its use in mild renal impairment! This comparison of the SPCs was selective and unbalanced with regard to facilitating a proper and full consideration of the comparative risk/benefit profile. The expediency of this omission became more apparent when on a previous page Trajenta was described as being generally well tolerated with an overall incidence of adverse events similar to that of placebo. If a direct comparison was being invited with the other DPP-4

inhibitors then a balanced and accurate comparison of the adverse event profile of all the medicines referred to should have been provided. Comparison of the warnings and precautions of the medicines mentioned was also clinically relevant and a serious omission. The selective use of regulatory documents such as SPCs to support a misleading promotional campaign was unacceptable.

The detailed response from Lilly and Boehringer Ingelheim is given below.

The Panel noted that the leavepiece was entitled 'Control and care matter'. The front cover set out the licensed indications for the product. The next three pages, ie the three page spread when the leavepiece was opened were headed 'Glycaemic control …', '… with a difference …' and 'Trajenta' respectively and set out various features of the medicine. The fifth page carried the prescribing information and the back page of the leavepiece featured a table comparing dosage recommendations of the currently available DPP-4 inhibitors according to degree of renal impairment.

The centre inside page, headed '… with a difference …', stated that Trajenta was the first DPP-4 inhibitor excreted primarily via the bile. The Panel did not consider that the claim implied that Trajenta was the first DPP-4 inhibitor as alleged. Health professionals would understand from the claim that Trajenta was the first in its class to be excreted primarily via the bile. No breach of the Code was ruled.

The claim relating to biliary excretion was followed by four bullet points each of which referred to a particular feature of Trajenta. The first bullet point stated '5% of the Trajenta dose is excreted via the kidney'. The second bullet point stated 'No dose adjustment'. In that regard Trajenta was different, as implied by the page heading, as the dose of all of the other DPP-4 inhibitors had to be adjusted in certain patient populations, for example those with declining renal functions. The Panel considered that the unqualified claim 'No dose adjustment' for Trajenta was not misleading and that it could be substantiated. No breach of the Code were ruled. The Panel did not consider that the claim suggested that saxagliptin could never be used without dose adjustment as alleged. In that regard the claim was neither misleading nor exaggerated. No breach of the Code was ruled. This was upheld by the Appeal Board following an appeal from the complainant. The Panel did not consider that the claim endangered patient safety as alleged. No breach of the Code was ruled.

The third bullet point stated 'No additional treatment-related renal monitoring required'. The Panel considered that this claim could be substantiated as the SPC clearly stated that 'For patients with renal impairment, no dose adjustment for Trajenta is required'. The Panel noted that NICE guidance on the management of type 2 diabetes stated that, regardless of the presence of nephropathy, kidney function should be measured annually. The Panel did not consider that the claim as issue suggested that regular monitoring should not be carried out. There was no additional monitoring to be done as a consequence of initiating Trajenta therapy. The Panel did not consider that the claim was misleading or that it was potentially dangerous as alleged. In the Panel's view the claim was not such that it did not encourage the rational use of Trajenta. No breach of the Code was ruled.

Below these bullet points and in a different font colour (orange) and type, was the sub-heading 'Appropriate for adult patients with type 2 diabetes at high risk of declining renal function'. The Panel considered that the presentation of the claim at issue was unlike the bullet points above which clearly related to differences between Trajenta and other DPP-4 inhibitors. The claim now at issue related to how Trajenta could be used. The Panel noted that Trajenta was the only available DPP-4 inhibitor which could be administered without any change in the dose to patients with any degree of renal failure. All the DPP-4 inhibitors could be used in patients at high risk of declining renal function. If patients were at high risk of declining renal function then once they had at least moderate renal failure sitagliptin and vildagliptin were no longer recommended. The dose of saxagliptin had to be reduced in moderate renal failure and used with caution in severe renal impairment. The Panel considered that as a product benefit of Trajenta the combination of the claim with a difference and the sub-heading was not unacceptable as alleged. If a patient was at high risk of declining renal function then it did not seem inappropriate, if a DPP-4 inhibitor was considered suitable, for that DPP-4 inhibitor to be Trajenta given the restrictions for use of the other DPP-4 inhibitors in renal impairment. No breach of the Code was ruled.

The sub-heading was followed by two further bullet points, 'Prescribe Trajenta 5mg once daily' and 'Can be taken with or without food'. The Panel noted the page heading '… with a difference …' and that all other DPP-4 inhibitors could be taken with or without food. Although in that regard Trajenta was no different from the other DPP-4 inhibitors the Panel considered that the page layout and presentation of the data was such that the lower half of the page would be seen as setting out the practical details for the prescribing of Trajenta in patients at high risk of declining renal function, ie 5mg once daily, with or without food. The Panel acknowledged that the page heading was '… with a difference ….' but considered that on balance given its positioning the claim 'Can be taken with or without food' was not misleading as alleged. No breach of the Code was ruled. This was upheld by the Appeal Board following an appeal from the complainant.

The Panel noted that health professionals would know to assess renal function before prescribing metformin and at least annually thereafter. As a result, the Panel did not consider that the claim 'No additional treatment-related renal monitoring required' suggested that such monitoring should not continue – only that the addition of Trajenta to metformin therapy would not necessitate additional monitoring. The Panel did not consider that the claim was misleading or potentially dangerous as alleged. No breach of the Code was ruled.

The Panel did not consider that given the absence of any information about the indications for the other DPP-4 inhibitors, the headline 'Glycaemic control… with a difference …' suggested that Trajenta had been specifically licensed for indications which were different to the other medicines, ie for the treatment of type 2 diabetes. The Panel did not consider that the leavepiece was misleading in that regard. No breach of the Code was ruled.

The Panel further did not consider that the presentation of the data suggested that the glycaemic control observed with Trajenta was somehow directly, solely or causally related to its route of excretion or the fact that no dosage adjustments were required in renal or hepatic failure. The Panel thus did not consider that the leavepiece was misleading in that regard. No breach of the Code was ruled.

The third inside page, ie the extreme right hand page of the leavepiece when opened out, was headed 'Trajenta' and included the claim 'Different – the first one dose, once daily DPP-4 inhibitor excreted primarily via the bile: no dose adjustment required'. The Panel noted, as above, that Trajenta was the first in class to be excreted primarily by the bile and to need no dose adjustment in any patient group. In that regard the Panel considered that the claim was not misleading or exaggerated. No breach of the Code was ruled.

The Panel noted that the leavepiece provided health professionals with a short introduction to Trajenta; it briefly described its efficacy vs placebo, set out practical consideration for its use (no dose adjustment or additional treatment-related renal monitoring) and stated the incidence of adverse events vs placebo. The back page featured a table detailing the dosage recommendations of currently available DPP-4 inhibitors according to the degree of renal impairment. The Panel noted that the data given in the table for saxagliptin was consistent with the particulars listed in the Onglyza SPC. The leavepiece did not purport to be a comprehensive comparison of Trajenta vs all of the other DPP-4 inhibitors. The Panel considered that the claim regarding the tolerability of Trajenta, 'Generally well tolerated – Trajenta, studied in over 4000 patients in clinical trials, has an overall incidence of adverse events that is similar to placebo' could be substantiated by the SPC to which it was referenced. The Panel did not consider that the omission of a full comparison of the SPCs for all the DPP-4 inhibitors meant that the leavepiece was unbalanced as alleged. The Panel did not consider that data from SPCs had been presented in an unacceptable way and in that regard the leavepiece was not misleading. No breach of the Code was ruled.

The Panel noted its rulings above and considered that neither Boehringer Ingelheim nor Lilly had failed to maintain high standards. No breach of the Code was ruled. This ruling was upheld by the Appeal Board following an appeal from the complainant. The Panel also did not consider that either company had brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

A general practitioner complained about a six page, gate-folded Trajenta (linagliptin) leavepiece entitled 'Control and care matter' (ref UK/TJR/00031). Trajenta was co-marketed by Boehringer Ingelheim Limited and Eli Lilly and Company Ltd for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults. It could be used as monotherapy or combination therapy.

COMPLAINT

The complainant alleged that the campaign by Boehringer Ingelheim and Lilly to sell Trajenta as a DPP-4 [dipeptidyl peptidase 4] inhibitor that was 'different' from others in the class appeared to rely on presenting promotional information that was variously misleading, unbalanced/selective, unsubstantiable and grossly exaggerated/distorted.

The complainant noted that the headline across pages 2 and 3 of the leavepiece at issue was 'Glycaemic control … with a difference …'. Page 3 featured a list of various differences which were wholly or partially incorrect with reference to the headline which invited a direct comparison with the other DPP-4 inhibitors referred to in the leavepiece.

The complainant submitted that, compared with medicines such as saxagliptin (Onglyza, co-marketed by Bristol-Myers Squibb and AstraZeneca) the only valid differences were that Trajenta: was the first DPP-4 inhibitor primarily excreted via the bile; that 5% of the Trajenta dose was excreted via the kidney and that no dosage adjustment was required for patients with hepatic impairment.

The complainant alleged that in the management of type 2 diabetics with renal impairment, Trajenta was not different or the first DPP-4 inhibitor, as was implied by the reference to no dose adjustment and no additional treatment-related renal monitoring required. Medicines such as saxagliptin could also be used with no dose adjustment in mild renal impairment. Trajenta could only claim to be different from saxagliptin with regard to its use specifically in patients with moderate and severe renal impairment where no dose adjustment was necessary; to suggest saxagliptin could never be used without dosage adjustment was misleading and exaggerated the facts and endangered patient safety.

The complainant alleged that the claim that no additional treatment-related renal monitoring was required with Trajenta was also misleading and potentially dangerous. This might be so when Trajenta was used as a monotherapy but not when used in combination with metformin; the use of Trajenta in combination with metformin was associated with prescribed schedules for renal monitoring according to guidelines issued by the National Institute for Health and Clinical Excellence (NICE). These guidelines also advocated regular renal monitoring of type 2 diabetics as a required aspect of good clinical practice; to suggest otherwise for the use of Trajenta

(even in monotherapy) was irresponsible.

The complainant noted that the leavepiece suggested that Trajenta was appropriate in adult patients with type 2 diabetes at high risk of declining renal function. If that was the case, how did this square with the claim that such patients could be managed with Trajenta without the need for additional treatment-related renal monitoring? How was the clinician to gauge any decline in renal function when using Trajenta if not by regular renal monitoring? The placement of the claim that Trajenta was appropriate in adult patients with type 2 diabetes at high risk of declining renal function, under the banner of glycaemic control with a difference, also suggested that Trajenta was different to the other DPP-4 inhibitors mentioned in this particular regard; this was not so given that all DPP-4 inhibitors could be used to treat this particular type of patient.

The complainant stated that in the absence of any information about the indication of the DPP-4 inhibitors mentioned, the headline 'Glycaemic control ... with a difference ...' also suggested that Trajenta had been specifically licenced for indications that were somehow different from the other DPP-4 inhibitors listed, ie the treatment of type 2 diabetes.

The complainant alleged that the way in which the above information was laid out, ie under the banner of 'Glycaemic control ... with a difference ...', suggested that the glycaemic control offered by Trajenta (ie reductions in HbA_{1C} vs placebo) was somehow directly, solely and causally related to the mode of excretion in bile, no requirement to adjust dosages or renal/hepatic monitoring; this could not be substantiated.

The complainant submitted that the leavepiece also stated that Trajenta was different from the other DPP-4 inhibitors in that it was the first one dose, once daily DPP-4 inhibitor excreted primarily via the bile: no dose adjustment required. This claim was general, all encompassing and misleading given that saxagliptin was also a once-daily medicine which did not require dose adjustment in mild renal impairment. Trajenta was also not different with regard to the implied claim that it only could be taken with or without food.

The complainant stated that as there were no published, randomized, controlled trials comparing the safety and efficacy of Trajenta with specifically sitagliptin, vildagliptin and saxagliptin the claim 'Glycaemic control ... with a difference ...' could not be substantiated. It appeared that the companies had contrived to specifically compare only those aspects of the summaries of product characteristics (SPCs) relating to dosing requirements according to renal impairment; which was what the commercial emphasis was but as explained above, even this had been deliberately misrepresented in the leavepiece with respect to saxagliptin and its use in mild renal impairment! This comparison of the SPCs was not only selective but was also unbalanced with regard to facilitating a proper and full consideration of the comparative risk/benefit profile as laid out in the full SPCs. The expediency of this omission became more apparent when on a previous page Trajenta was described as being generally well tolerated with an overall incidence of adverse events similar to that of placebo. If a direct comparison was being invited with the other DPP-4 inhibitors then it was incumbent upon the companies to provide a balanced and accurate comparison of the adverse event profile of all the medicines referred to. Comparison of the warnings and precautions of the medicines mentioned was also clinically relevant and a serious omission. The selective cut-and-pasting of regulatory documents such as SPCs in support of a misleading promotional campaign went beyond what was acceptable or desirable.

The complainant stated that given this very deliberate intent to confuse health professionals, the companies might as well have called the medicine 'Tangenta'; a more apt brand name given the questionable basis upon which the difference offered by Trajenta, compared with other DPP-4 inhibitors, was being promoted.

When writing to Boehringer Ingelheim and Lilly, the Authority asked the companies to respond in relation to Clauses 2, 7.2, 7.4, 7.9, 7.10 and 9.1 of the Code.

RESPONSE

Boehringer Ingelheim and Lilly submitted a joint response and explained that the leavepiece at issue introduced health professionals to Trajenta. It was used in promotional calls and meetings by primary and secondary care representatives and health service managers in September and was recalled in October during which time approximately 11,000 copies were distributed.

The layout of the item was intended to be read, in order, starting with the front cover, where the approved therapeutic indications for Trajenta were clearly stated, in full, at the first product mention. Page 2 provided the supporting efficacy data in terms of HbA_{1C} reductions vs placebo for the three main indications and ran into page 3 which described Trajenta as a DPP-4 inhibitor, outlined its main features and identified a typical patient in whom Trajenta might be used. Page 4 provided a product summary and reiterated the approved indications and outlined the summary safety information. Page 5 contained prescribing information and references and page 6 featured a table which compared the dose recommendations for DPP-4 inhibitors in renal impairment taken from the SPCs for all DPP-4 inhibitors currently approved for use in the UK.

The companies submitted that the claim 'Glycaemic control ... with a difference' was supported on page 3 by a number of claims. As noted by the complainant, Trajenta had valid differences: the first DPP-4 inhibitor excreted primarily via the bile; only 5% Trajenta dose excreted via the kidney and no dose adjustment for patients with hepatic impairment. Additional differences included no dose adjustment required for patients with any degree of renal impairment (the focus of the chart on page 6) and that no additional monitoring of renal function was necessary as a

consequence. These differences arose from the metabolism, excretion and elimination pathways for Trajenta (excreted largely unchanged with minimal metabolism in the body including hepatic or renal metabolism and eliminated via the faeces through excretion in the bile with only 5% of the administered oral dose excreted via the kidney). This was clearly different from the metabolic and excretory routes of the other DPP-4 inhibitors and allowed Trajenta to be administered as a single 5mg dose without dosage adjustment in any of the special patient populations stated within the SPC. These claims were referenced to the product SPC and other publications supporting pharmacokinetic data for Trajenta which supported the link between Trajenta's unique pharmacokinetic characteristics amongst the DPP-4 inhibitor class and the lack of any requirement for dosage adjustment in special patient populations including renal and hepatic impairment and the elderly.

Boehringer Ingelheim and Lilly considered that the claims were genuine and supportable and not in breach of Clauses 7.2, 7.4, 7.9 and 7.10.

With regard to the claim '.... No additional treatment related renal monitoring required' Boehringer Ingelheim and Lilly submitted that 'additional' used here was intended to refer specifically to any extra monitoring directly consequential on the use of Trajenta; the claim was referenced to the Trajenta SPC. This referred to monitoring in addition to routine monitoring as recommended by NICE, for example, of which none was required. Agents which required any form of dose adjustment as a consequence of decline in renal function would of necessity require monitoring. Annual checks or 'routine care' were not specifically defined and might not be adequate in the clinical setting, particularly in individuals with rapidly declining renal function or who were approaching critical points in terms of specific measurements of renal function, eg estimated glomerular filtration rate (eGFR) 30-45ml/min/1.73m2.

The companies stated that for Trajenta, no additional renal monitoring was required in this situation because there was no need for the dose to be adjusted in mild, moderate or severe renal impairment. This applied to Trajenta only; the companies submitted that they were not suggesting that it was 'not required' for any other medicines used in combination with Trajenta or that 'routine care' renal monitoring could be ignored in terms of general management of patients with type 2 diabetes prescribed Trajenta. The companies agreed that patients with signs of declining renal function needed to be more closely monitored; however, this was independent of, and not a requirement consequent on, their use of Trajenta.

With regard to saxagliptin, the only reference made to prescribing this product in patients with renal impairment was taken directly from Section 4.2 of the Onglyza SPC. The companies submitted that they had neither suggested nor claimed that 'saxagliptin could never be used without dosage adjustment' as alleged.

Boehringer Ingelheim and Lilly submitted that the claim on page 3 (the centre page when the leavepiece was fully opened) '... Appropriate for adult patients with type 2 diabetes at high risk of declining renal function' provided the link between the DPP-4 inhibitor and Trajenta features section above and the Trajenta prescribing section below. When the leavepiece was open, as it would need to be to view this page, the page to the right included the summarised therapeutic indications for Trajenta and which was the next logical section to be read. The therapeutic indications section of the SPC had already been clearly presented on the front cover of the leavepiece. The companies expected that the reader should therefore have gained a good understanding of the therapeutic indications for Trajenta on this basis, having now been exposed to them twice on this single six page item.

The companies agreed that patients for whom the DPP-4 inhibitor class was currently considered appropriate, for example as per NICE guidelines, were advancing in their diabetes and were likely to have signs of declining renal function. The companies submitted that they had not claimed that other DPP-4 inhibitors could not be used in these circumstances but rather that Trajenta could reasonably be used here in the manner in which it had been presented.

Boehringer Ingelheim and Lilly stated that the claim prefaced 'Different' should be read in its entirety, ie 'the first one dose, once daily DPP-4 inhibitor excreted primarily via bile'. Each phrase was not intended to be a stand-alone statement of difference and to do that was to take this out of context.

The companies considered that the comparator table on the back cover was sufficiently balanced as it represented and drew on the publicly available data from the same section of each product SPC for all currently available DPP-4 inhibitors. There were no randomized, controlled trial head-to-head data comparing the efficacy and safety of the various DPP-4 inhibitors currently available in the UK. However, the table aimed to compare dosing recommendations in renal impairment as stated in the header. In the absence of other comparator data, the companies considered a comparison of data in the various product SPCs was the most fair and relevant way to make such comparisons between products in the same treatment class. The wording used was as it appeared in Section 4.2 of each SPC, including the specific wording for use in renally impaired patients. Each product, other than Trajenta, was represented in the same way in terms of font size, colour, shading etc as the companies were not permitted to imply any advantage/disadvantage nor make any claims for any medicine other than their own. The intention was to present the factual data. Boehringer Ingelheim and Lilly submitted that they had included exact wording in the table; where the information was detailed, as was the case for saxagliptin, additional information was included in the footnote so the table was not too text heavy and did not draw attention inappropriately to one particular medicine. Where the detail was not included in the SPC, for example specific measurements or levels of renal impairment other than broad categories, mild,

moderate or severe or reference to creatinine clearance for guidance, the leavepiece did not specify any more than was actually included in the SPC. This was intentional in order to provide a fair and balanced comparison between all product SPCs. The SPCs were the most relevant source of information for conducting a comparison of this nature of the product class and were the acknowledged reference source for information on prescribing in special patient populations and product assessment provided a consistent and highly regulated approach in the manner in which each product was assessed while also allowing the marketing authorization holder to update the information contained in the SPC as and when important new data become available. As stated in the title of the table, this was intended as a comparison of DPP-4 inhibitors for use in renal impairment only and did not purport to compare other features such as the different therapeutic indications for each treatment.

The companies submitted that Trajenta, as outlined above, could be used in patients with mild, moderate or severe renal impairment, irrespective of renal function. Decisions with regard to dose adjustment for any other agents used in combination with Trajenta would be made independently of decisions for Trajenta because different prescribing restrictions pertained for each and would be based on individualised patient assessment.

The companies considered the summary table presented an accurate, clear and balanced view of prescribing the different DPP-4 inhibitors in renal impairment, based on SPC evidence.

The companies stated that on page 4 of the leavepiece, Trajenta was described as 'Generally well tolerated' and this was qualified by wording summarised from Section 4.8 of the SPC which stated 'Trajenta has been evaluated overall in 4,687 patients with type 2 Diabetes Mellitus of which 4,040 received the target dose of 5mg' and 'In the pooled analysis of the placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo was similar to Trajenta 5mg'. In the leavepiece this had been summarised to 'Trajenta, studied in over 4,000 patients in clinical trials has an overall incidence of adverse events that is similar to placebo'. The companies noted that materials for newly licensed products were subject to pre-vetting by the Medicines and Healthcare products Regulatory Authority (MHRA) and the claim 'Generally well tolerated' and text was agreed after feedback from the MHRA as being appropriate as a summary safety statement for a newly licensed DPP-4 inhibitor.

In summary Boehringer Ingelheim and Lilly considered that they had presented Trajenta in an accurate, balanced fair, objective and unambiguous manner based on an up-to-date evaluation of the evidence. They did not intend to mislead by distortion, exaggeration or undue emphasis and preferred to focus on the factual data, all of which was capable of substantiation. The safety data was presented in a clear manner and reflected the SPC as agreed with the MHRA during the pre-vetting process. As such the companies did not consider the leavepiece was in breach of Clauses 7.2, 7.4, 7.9 or 7.10. Boehringer Ingelheim and Lilly submitted that they had maintained high standards in the presentation of the leavepiece and had not undertaken activities or presented materials which brought discredit upon or reduced confidence in the pharmaceutical industry. The companies denied a breach of Clauses 2 or 9.1.

PANEL RULING

The Panel noted that the leavepiece was entitled 'Control and care matter'. The front cover set out the licensed indications for the product. The next three pages of the leavepiece ie the three page spread when the leavepiece was opened were headed 'Glycaemic control …', '… with a difference …' and 'Trajenta' respectively and set out various features of the medicine. The fifth page carried the prescribing information and the back page of the leavepiece featured a table comparing dosage recommendations of the currently available DPP-4 inhibitors according to degree of renal impairment.

The centre inside page, headed '… with a difference …', stated that Trajenta was the first DPP-4 inhibitor excreted primarily via the bile. The Panel did not consider that the claim implied that Trajenta was the first DPP-4 inhibitor as alleged. The leavepiece was targeted at health professionals who, in the Panel's view, would understand from the claim that Trajenta was the first in its class to be excreted primarily via the bile. In addition the audience would be aware of the other DPP-4 inhibitors on the market. Details of these were given on the back page of the leavepiece. The Panel did not consider that the claim was misleading. No breach of Clause 7.2 was ruled.

The claim relating to biliary excretion was followed by four bullet points each of which referred to a particular feature of Trajenta. The first bullet point stated '5% of the Trajenta dose is excreted via the kidney'. The second bullet point stated 'No dose adjustment'. In that regard Trajenta was different, as implied by the page heading, as the dose of all of the other DPP-4 inhibitors had to be adjusted in certain patient populations, for example those with declining renal functions. The Panel considered that the unqualified claim 'No dose adjustment' for Trajenta was not misleading and that it could be substantiated. No breach of Clauses 7.2 and 7.4 were ruled. The Panel did not consider that the claim suggested that saxagliptin could never be used without dose adjustment as alleged. In that regard the claim was neither misleading nor exaggerated. No breach of Clauses 7.2 and 7.10 were ruled. This ruling was appealed by the complainant. The Panel did not consider that the claim endangered patient safety as alleged. No breach of Clause 7.9 was ruled. This ruling was not appealed.

The third bullet point stated 'No additional treatment-related renal monitoring required'. The Panel considered that this claim could be substantiated as the SPC clearly stated that 'For patients with renal impairment, no dose adjustment for Trajenta is

required'. The Panel noted that NICE guidance on the management of type 2 diabetes stated that, regardless of the presence of nephropathy, kidney function should be measured annually. The Panel did not consider that the claim as issue suggested that regular monitoring should not be carried out. In the Panel's view health professionals would be well aware of the need to monitor renal function in type 2 diabetes; the claim at issue informed them that there was no additional monitoring to be done as a consequence of initiating Trajenta therapy. The Panel did not consider that the claim was misleading or that it was potentially dangerous as alleged. In the Panel's view the claim was not such that it did not encourage the rational use of Trajenta. No breach of Clauses 7.2 and 7.10 were ruled.

Below these bullet points and in a different font colour (orange) and type, was the sub-heading 'Appropriate for adult patients with type 2 diabetes at high risk of declining renal function'. The Panel considered that the presentation of the claim at issue was unlike the bullet points above which clearly related to differences between Trajenta and other DPP-4 inhibitors. The claim now at issue related to how Trajenta could be used. The Panel noted that Trajenta was the only one of the available DPP-4 inhibitors which could be administered without any change in the dose to patients with any degree of renal failure. All the DPP-4 inhibitors could be used in patients at high risk of declining renal function. If patients were at high risk of declining renal function then once they had at least moderate renal failure sitagliptin and vildagliptin were no longer recommended. The dose of saxagliptin had to be reduced in moderate renal failure and used with caution in severe renal impairment. The Panel considered that as a product benefit of Trajenta the combination of the claim with a difference and the sub-heading was not unacceptable as alleged. If a patient was at high risk of declining renal function then it did not seem inappropriate, if a DPP-4 inhibitor was considered suitable, for that DPP-4 inhibitor to be Trajenta given the restrictions for use of the other DPP-4 inhibitors in renal impairment. No breach of Clause 7.2 was ruled.

The sub-heading was followed by two further bullet points, 'Prescribe Trajenta 5mg once daily' and 'Can be taken with or without food'. The Panel noted the page heading '… with a difference…' and that all other DPP-4 inhibitors could be taken with or without food. Although in that regard Trajenta was no different from the other medicines in the same class, the Panel considered that the page layout and presentation of the data was such that the lower half of the page would be seen as setting out the practical details for the prescribing of Trajenta in patients at high risk of declining renal function ie 5mg once a daily, with or without food. The Panel acknowledged that the page heading was '… with a difference ….'. But considered that on balance given its positioning the claim 'Can be taken with or without food' was not misleading as alleged. No breach of Clause 7.2 was ruled. This ruling was appealed by the complainant.

The Panel noted the complainant's comments about the use of Trajenta in combination with metformin. The Panel noted that metformin was well established in the treatment of type 2 diabetes and so health professionals would be familiar with the need for renal function to be assessed before prescribing and at least annually thereafter. As a result, the Panel did not consider that the claim 'No additional treatment-related renal monitoring required' suggested that such monitoring should not continue – only that the addition of Trajenta to metformin therapy would not necessitate additional monitoring. The Panel did not consider that the claim was misleading or that it was potentially dangerous as alleged. In the Panel's view the claim was not such that it did not encourage the rational use of Trajenta in combination with metformin. No breach of Clauses 7.2 and 7.10 were ruled.

The Panel did not consider that given the absence of any information about the indications for the other DPP-4 inhibitors, the headline 'Glycaemic control… with a difference…' suggested that Trajenta had been specifically licensed for indications which were different to the other medicines, ie for the treatment of type 2 diabetes. The Panel did not consider that the leavepiece was misleading in that regard. No breach of Clause 7.2 was ruled.

The Panel further did not consider that the presentation of the data within the leavepiece suggested that the glycaemic control observed with Trajenta was somehow directly, solely or causally related to its route of excretion or the fact that no dosage adjustments were required in renal or hepatic failure. The Panel thus did not consider that the leavepiece was misleading in that regard. No breach of Clause 7.2 was ruled.

The third inside page, ie the extreme right hand page of the leavepiece when opened out, was headed 'Trajenta' and included the claim 'Different – the first one dose, once daily DPP-4 inhibitor excreted primarily via the bile: no dose adjustment required'. The Panel noted, as above, that Trajenta was the first in class to be excreted primarily by the bile and to need no dose adjustment in any patient group. In that regard the Panel considered that the claim was not misleading or exaggerated. No breach of Clauses 7.2 and 7.10 were ruled.

The Panel noted that the leavepiece provided health professionals with a short introduction to Trajenta; it briefly described its efficacy vs placebo, set out practical consideration for its use (no dose adjustment or additional treatment-related renal monitoring) and stated the incidence of adverse events vs placebo. The back page featured a table detailing the dosage recommendations of currently available DPP-4 inhibitors according to the degree of renal impairment. The Panel noted that the data given in the table for saxagliptin was consistent with the particulars listed in the Onglyza SPC. The leavepiece did not purport to be a comprehensive comparison of Trajenta vs all of the other DPP-4 inhibitors. The Panel considered that the claim regarding the tolerability of Trajenta, 'Generally well tolerated – Trajenta, studied in over 4000 patients in

clinical trials, has an overall incidence of adverse events that is similar to placebo' could be substantiated by the SPC to which it was referenced. The Panel did not consider that the omission of a full comparison of the SPCs for all the DPP-4 inhibitors meant that the leavepiece was unbalanced as alleged. The Panel did not consider that data from SPCs had been presented in an unacceptable way and in that regard the leavepiece was not misleading. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above and considered that neither Boehringer Ingelheim nor Lilly had failed to maintain high standards. No breach of Clause 9.1 was ruled. This ruling was appealed by the complainant. The Panel also did not consider that either company had brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

APPEAL BY THE COMPLAINANT

The complainant was disappointed that the Panel had considered that the leavepiece in question was faultless. The complainant was inclined to accept this were it not for the fact that the basis for this appeared to be inconsistent.

The complainant stated that on one hand the Panel clearly recognised that some of the claims highlighted features of Trajenta that were different from other DPP-4 inhibitors and ruled this was acceptable and could be substantiated. However, the Panel did not consider that the claim that Trajenta 'Can be taken with or without food', which appeared under the same banner highlighting '… with a difference …' (compared with other DPP-4 inhibitors), was misleading and, evidently, relied on its own subjective criteria of 'balance' rather than the more objective fact that this claim, as presented, was clearly misleading and suggested that Trajenta, unlike other DPP-4 inhibitors, could be taken with or without food.

The complainant stated that whilst in the context of the whole complaint this might seem a relatively minor point, it brought into question the Panel's objectivity in relation to some of the other rulings. The complainant therefore appealed the Panel's ruling of no breach of Clause 7.2.

As the focus of the leavepiece was to highlight differences with other DPP-4 inhibitors, the complainant also appealed the rulings that the leavepiece did not suggest that saxagliptin could never be used without dose adjustment in patients with renal failure. This claim was implicit in the manner in which the information that Trajenta required no dose adjustment was presented early on under the banner of 'difference' but the clarifying details regarding saxagliptin were presented on the last page; it was possible that health professionals might not read the information presented in the SPC comparison on the last page and would therefore be likely to be misled up to that point.

The complainant appealed the ruling of no breach of Clause 9.1 for the above reasons.

RESPONSE FROM THE BOEHRINGER INGELHEIM and LILLY

Boehringer Ingelheim and Lilly had no additional comments.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant had no additional comments.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'No dose adjustment' appeared as a bullet point on the centre inside page, headed '… with a difference …'. The Appeal Board noted that no dosage adjustment of Trajenta was necessary in patients with any degree of renal insufficiency; this was different to other DPP-4 inhibitors, including saxagliptin, as listed on page 6 of the leavepiece. The Appeal Board did not consider that the claim suggested that saxagliptin could never be used without dose adjustment as alleged. In that regard the claim was neither misleading nor exaggerated. The Appeal Board upheld the Panel's ruling of no breach of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

The Appeal Board noted that the lower half of the centre inside page was printed in a different font colour (orange) and type face to the top of the page and it started with the subheading 'Appropriate for adult patients with type 2 diabetes at high risk of declining renal function'. Below this subheading there were two bullet points 'Prescribe Trajenta 5mg once daily' followed by the bullet point at issue 'Can be taken with or without food'. The Appeal Board noted that all other DPP-4 inhibitors could be taken with or without food. However, the Appeal Board considered that this bullet point described the practical details for the prescribing of Trajenta, ie that it could be taken with or without food. In the Appeal Board's view, the bullet point would not be read in the context of the heading at the top of the page '… with a difference …'. It considered that the page had been separated into two.

The Appeal Board considered that given its position on the page and the visual differences in colour and typeface the claim 'Can be taken with or without food' was not misleading as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clauses 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and considered that neither Boehringer Ingelheim nor Lilly had failed to maintain high standards. The Appeal Board upheld the Panel's ruling of no breach of Clause 9.1. The appeal on this point was unsuccessful.

Complaint received **2 November 2011**

Case completed **19 January 2012**

CASE AUTH/2451/11/11

MERCK SERONO v SANDOZ

Omnitrope patient support items

Merck Serono complained about a soft toy, water bottle and backpack offered as patient support items by Sandoz in relation to its product Omnitrope (somatropin).

Merck Serono did not consider that the items were related to the treatment of growth hormone deficiency. Merck Serono was unable to find scientific evidence that concluded that the items, either individually or as part of a package, were linked to improved adherence. Merck Serono was concerned that the backpack cost more than £6.

The detailed response from Sandoz is given below.

The Panel had to decide whether the provision of each item (the backpack, soft toy and water bottle) individually met the requirements of the Code regarding patient support items. The Panel considered that the supplementary information indicated that an acceptable patient support item need not necessarily be medical in nature but should be supplied for a clear specific purpose related to the disease in question.

The Panel recognised the difficulties with a child adhering to a treatment regime that involved daily injections. The Panel noted that the parent/carer testimonies discussed the use of rewards, or comforters. None referred to the soft toy at issue. The Panel noted the letters from endocrine specialists and considered that, on balance, these supported Sandoz's view that a toy such as the one at issue might be used as a comforter in the initial stages of growth hormone treatment injections to aid compliance. It could be argued that providing a soft toy for a child to cuddle when having an injection when such treatment was required every day would directly benefit patient care. On balance no breach of the Code was ruled.

Whilst accepting that hydration promoted good health, the Panel did not consider that provision of the water bottle as a patient support item was directly related to the condition under treatment, and ruled a breach of the Code in that regard.

With regard to the rucksack the Panel noted that Omnitrope had to be stored at 2-8˚C irrespective of whether the cartridge had been opened or not. The rucksack would not be appropriate for storing Omnitrope. The Panel was thus not satisfied that the rucksack in question was related to the treatment of growth hormone deficiency or otherwise directly benefitted patient care. A breach was ruled.

The Panel noted that the unit cost for each of the items at issue was £6 or less plus VAT and thus inexpensive as defined by the Code and no breach was ruled.

Merck Serono Limited complained about a soft toy, water bottle and backpack offered as patient support items by Sandoz Ltd in relation to its product Omnitrope (somatropin). Omnitrope was indicated for the treatment of a number of growth disturbances in infants, children and adolescents and hormone replacement therapy in adults.

The items in question were also referred to in Omnitrope promotional material (including exhibition stand posters, a display unit containing the items, leavepieces and a video).

COMPLAINT

Merck Serono alleged that Sandoz had breached Clause 18.2 of Code, the supplementary information to which stated 'Items which may be made available to patients … should be inexpensive and related to either the condition under treatment or general health. No item for use by patients must be given for the purpose of encouraging patients to request a particular medicine'.

Merck Serono did not consider that the items in question were related to the treatment of growth hormone deficiency. It had asked Sandoz to withdraw the items, all references to them and not to distribute them to patients on initiation of Omnitrope. In response, Sandoz claimed that the items supported adherence and were related to the condition under treatment and general health, therefore did not breach Clause 18.2.

Merck Serono had reviewed the references provided and undertaken its own literature search and was unable to find scientific evidence which concluded that the items, either individually or as part of a package, were linked to improved adherence.

Sandoz also stated '… the backpack aids adherence by allowing the patient to store and transport their GH [growth hormone] and supporting items from one destination to another, including repeat visits, ensuring that they have all the items they need to perform each injection on a daily basis regardless of their location'.

Merck Serono was concerned that the backpack in question (which did not have a built in cool bag component and would definitely cost more than £6) was used to transport Omnitrope which, according to its summary of product characteristics (SPC), required refrigeration. In addition, no cost data had been provided by Sandoz in response to Merck Serono's request. Merck Serono did not agree with the Sandoz response.

Merck Serono was not aware that other companies were providing these items as stated by Sandoz. No

other growth hormone company was demonstrating or referring to these items at the European Society for Paediatric Endocrinology conference which was held in Glasgow in September 2011.

RESPONSE

Sandoz explained that the complaint from Merck Serono and further correspondence had specifically related to three patient support items, the soft toy (termed the comforter or soft dog by Sandoz), the water bottle and backpack. There had been no written correspondence sent to Sandoz which related to '… promotional materials referring to these patient support items including the exhibition stand posters, a display unit containing the items, leavepieces and a video'. Sandoz therefore considered that it had not had an opportunity to discuss these items through inter-company dialogue so it would just focus on the specific items in question.

The patient support package (collectively known as the Sproutz) offered to patients prescribed Omnitrope comprised of support items which were designed to aid adherence and general health. The backpack, comforter (soft dog) and water bottle formed an integral part of the overall support package.

Growth hormone deficiency was a chronic condition and required patients to inject growth hormone daily. Sandoz submitted that adherence and concordance to growth hormone therapy could be poor and it had been suggested that non-adherence might be as high as 36% to 49%. The many causes of non-adherence fell into two overlapping categories, intentional and unintentional. Intentional non-adherence could be associated with perceptual barriers, for example patients' beliefs and preferences, and unintentional non-adherence with practical barriers, for example capacity and resources. It was these factors that influenced a patient's ability to adhere to the agreed treatment. Published guidelines recognised that interventions might help with non-adherence and while Sandoz appreciated that these interventions were not solely material or physical items, the concept that such items might improve adherence was well recognised in the field of endocrinology. A number of letters from endocrine key opinion leaders relating to this point were provided by Sandoz.

The comforter was an intervention provided to remove perceptual barriers to daily growth hormone treatment as the support item was designed to comfort and reduce the fear associated with daily injections and thus aimed to limit intentional non-adherence. The rucksack was designed to reduce the likelihood of those who were unintentionally non-adherent by removing the practical barriers related to growth hormone treatment as it provided patients with somewhere to store and transport their medication including the supplied cool bag, a validated cool bag required to store the medicine between 2-8˚C. The water bottle, while less related to adherence, supported the Water in School is Cool Campaign that was appointed by the Department of Health to research and develop the Food in Schools Water Provision guidance. This initiative specifically stated that 'drinking regularly throughout the day is vital not only for healthy bladders and bowels, but also for general health and wellbeing'. Sandoz therefore considered that the availability of the water bottle for patients being treated with Omnitrope gave patients the ability to keep hydrated throughout the day and ultimately supported their general health.

Sandoz also referred to some statements which had been posted on The Child Growth Foundation website by parents/carers of children receiving growth hormone replacement therapy. Sandoz submitted that these demonstrated the fear and pain associated with the growth hormone injections and the interventions parents used to help their child comply with treatment:

> 'Hi …, our son is nearly 4 and has been on treatment since May. Initially it was horrendous as we used the easy pod and he used to scream every night. We tried to give him it in his sleep as we are all distressed but then he was having trouble sleeping. We were told to hold him down but we couldn't cope so stopped treatment for a week and chose another device, Genotropin. We are now in a routine and he has this before his bath and we did give him a toy every night (cheap toys from pound shop) and this did the trick. I never thought we would be where we are now and even questioned if we should continue. But what choice do we have. … has grown 5cm in this short time. Keep with it. If you want any further advice or to talk via email I will happily forward my email. It may be worth considering another device as I think sometimes association of pain with the initial device is a hurdle. There is one device without a needle. We inject … in his bottom every night as his legs seemed to feel the pain more plus if your partner holds him they cannot see what is happening. …'.
>
> 'Hi, my daughter although older (8yrs) has a special injection sweet jar, where after her injection she gets to choose 1 sweet, this stopped the tears almost immediately!! We think of it as reward rather than bribery and it works for her, also we involve her in choosing the sweets and make it very clear that they are for brave children. Good luck anything is worth a try, …'
>
> 'Hi my son is now 8 (MPHD) and we started injections at 6. We chose the zomacton pen as it was needle free. Initially it caused problems - some bruising and bleeding and he was terrified of the injections - screamed and refused to cooperate. As a result for over a year we injected in his sleep. This worked for us as it was less stressful and I am pleased to say he is now over 50th centile, he started below the graphs. Now he self-injects every night and only asks for me to do it if he is unwell. I wanted to write because we certainly found it really difficult at first but he is now growing and self-injecting. We did not put any pressure on him we felt he had enough to cope with medically although we were very open and he took the decision when to start self-injecting. Hang in there it will get easier.'

Sandoz submitted that one further key point was that the patient support items should only be given to patients once they had been prescribed Omnitrope, they were not to be used as an incentive for the patient to choose Omnitrope over other available treatments. This decision should be based on the needs of the patient identified by the prescribing clinician after discussion with the parent or guardian as outlined in the National Institute for Health and Clinical Excellence (NICE) Guidance T1A88. In addition, Sandoz stated that it had evidence to show that similar items were provided by other growth hormone companies; a number of photographs of items on exhibition stands were provided.

Sandoz considered that the patient support items offered to patients that had been prescribed Omnitrope were related to the condition under treatment or general health as they provided the parent or carer with items to help ensure that their child adhered to their treatment. Sandoz considered that the materials in question were not in breach of Clause 18.2. As a company it was committed to supporting patients and through interaction and guidance from clinicians in this field considered that if these items were withdrawn by pharmaceutical companies this would have a detrimental effect on the overall treatment of children.

In response to the request for further information Sandoz provided copies of materials referring to the three items at issue, the backpack, soft toy and water bottle. The company stressed again that it did not consider that it had an opportunity to discuss the exhibition stand panels, leavepieces and DVD through inter-company dialogue with Merck Serono as these items were only raised in the correspondence to the PMCPA and not to Sandoz.

The patient support package offered by Sandoz was only given to patients once they have been prescribed Omnitrope. The decision of which growth hormone to use was based on the needs of the patient identified by the prescribing clinician after discussion with the parent or guardian as outlined in the NICE Guidance T1A88. The Omnitrope support package was subsequently provided to patients either by the nurse from the homecare company or by the health professional, primarily the endocrine specialist nurse.

PANEL RULING

The Panel noted that Clause 18.2 stated that health professionals may be provided with items which were to be passed on to patients and which were part of a formal patient support programme, the details of which had been appropriately documented and certified in advance as required by Clause 14.3. The items provided must be inexpensive and directly benefit patient care. The supplementary information to Clause 18.2 Patient Support Items stated, *inter alia*, inexpensive meant one costing the donor company no more than £6 excluding VAT. Examples were included such as a pedometer as part of a scheme to encourage exercise, perhaps for obese patients.

Merck Serono referred to the supplementary information to Clause 18.2 Items Given to Patients which stated that items which may be made available to patients, for example, by completing a request card enclosed with a medicine, should be inexpensive and related to either the condition under treatment or general health. Sandoz described the items as patient support items but also referred to their acceptability in relation to items given to patients and general health.

When responding to the request for additional information Sandoz was clear that the items at issue were patient support items, referring to them as such three times. The Panel considered them accordingly in relation to the requirements for patient support items.

The Panel had to decide whether the provision of each item (the backpack, soft toy and water bottle) individually met the requirements of the Code regarding patient support items. The Panel considered that use of a pedometer as part of a scheme to encourage exercise, one of the examples in the supplementary information of an acceptable patient support item, indicated that such items need not necessarily be medical in nature but should be supplied for a clear specific purpose related to the disease in question. The Panel had not been supplied with all of the material describing the patient support programme and its use other than photographs of some of the materials, a poster, reply paid card and a pen training DVD, and one of each of the three items at issue.

The Panel noted from Sandoz's submission that the items at issue in this case, the backpack, soft toy and water bottle, formed part of the overall support package. It appeared that Sandoz also supplied a cool bag about which there was no complaint.

The Panel recognised the difficulties in ensuring that a child adhered to a treatment regime that involved daily injections. The Panel noted that the parent/carer testimonies provided by Sandoz discussed the use of rewards, including sweets and toys as rewards or comforters. None referred to the soft toy at issue. The Panel noted the letters from endocrine key opinion leader specialists provided by Sandoz. The Panel considered that, on balance, these supported Sandoz's view that a toy such as the one provided by Sandoz might be used as a comforter in the initial stages of treatment with growth hormone injections to aid compliance in children. It could be argued that providing a soft toy for a child to cuddle when having an injection when such treatment was required every day would directly benefit patient care. On balance no breach of Clause 18.2 was ruled.

In relation to the provision of the water bottle, the Panel noted that a letter from a clinical nurse specialist in endocrinology stated that hydration was essential to promote good health 'especially when [a child was] growth hormone deficient'. Sandoz had not submitted any clinical evidence that hydration was particularly important in patients with growth hormone deficiency. Whilst accepting that hydration

promoted good health, the Panel did not consider that provision of the water bottle as a patient support item was directly related to the condition under treatment, and ruled a breach of Clause 18.2 in that regard.

With regard to the rucksack the Panel noted that Omnitrope had to be stored at 2-8˚C irrespective of whether the cartridge had been opened or not. The rucksack would not be appropriate for storing Omnitrope. It appeared that Sandoz provided a cool bag for that purpose. The Panel was thus not satisfied that the rucksack in question was related to the treatment of growth hormone deficiency or otherwise directly benefitted patient care. A breach of Clause 18.2 was ruled.

The Panel noted that Sandoz had submitted invoices that indicated that the unit cost for each of the items at issue was £6 or less plus VAT and was thus inexpensive as defined by the supplementary information to Clause 18.2. No breach of Clause 18.2 was ruled in that regard.

The Panel noted that Merck Serono had referred to Omnitrope promotional material (including exhibition stand posters, a display unit containing the items, leavepieces and a video) which contained reference to the patient support items at issue. Sandoz submitted that these items were not raised during inter-company dialogue, so did not refer to them in its response to the Authority. The Panel noted that the rulings of breaches of the Code regarding the patient support items above would apply to any other material that referred to the water bottle or rucksack. The question of whether or not inter-company dialogue had taken place was thus irrelevant in this regard.

Complaint received **3 November 2011**

Case completed **17 January 2012**

ANONYMOUS v PIERRE FABRE

Conduct of representative

An anonymous and non contactable complainant alleged that a representative from Pierre Fabre had sent unsolicited emails to NHS colleagues without consent. The complainant alleged that within the emails, of which the complainant did not have copies, the representative discussed and asked to meet to help set up 'oral chemotherapy' clinics for use within clinicians' respective departments.

The complainant considered that the emails were, and could be perceived as, promotional and no prescribing information was attached. The complainant asked if they had been formally certified and whether the representative had obtained permission from oncology pharmacists to communicate with them by email.

The complainant stated that he/she was quite concerned that the pharmaceutical industry, and this representative in particular, appeared not to have been briefed specifically about the use of email; the Code was very clear about the potential issues regarding emailing customers, and stressed that it was completely inappropriate to mention company products in emails of this nature.

The complainant asked if the representative had recently undergone any refresher training on the Code that stressed the importance of certifying all promotional material.

The detailed response from Pierre Fabre is given below.

The Panel considered that the complaint solely concerned emails which referred to oral chemotherapy clinics. The Panel noted Pierre Fabre's submission that such clinics were not a company product or service but part of a re-designed patient treatment pathway which was the responsibility of, and driven by, individual hospital trusts. In that regard the Panel considered that emails which did not refer directly or indirectly to oral chemotherapy clinics were not the subject of complaint.

The Code stated, *inter alia*, that email must not be used for promotional purposes except with the prior permission of the recipient. The Panel noted Pierre Fabre's submission that it did not distribute promotional material by email and so did not subscribe to email directories or otherwise provide representatives with email addresses from proprietary listings. Any email address used had been willingly provided by the recipient to facilitate communication in relation to, *inter alia*, meetings and appointments. The Panel noted that the relevant supplementary information explained that an enquiry received by email could be responded to by email without specific permission; consent to do so being implied.

The Panel examined the two sets of email traffic at issue. In the first series the representative sought a meeting to discuss potential company support for an oral chemotherapy service. There was a general reference to patient support packs. The Panel queried whether it was appropriate to refer, albeit generally, to patient support items in such an email as it might be seen as an inducement to gain an interview contrary to the Code. However, no details were provided about the items and they were not the subject of the complaint. There was no reference direct or indirect to Pierre Fabre's products. The second series of emails discussed a recent meeting where streamlining the patient pathway and best practice had been discussed. Again there was no reference to Pierre Fabre's products.

Whilst the Panel had some concerns about the emails it did not consider that either the first or second series were promotional on the narrow ground alleged. There was no reference direct or implied to Pierre Fabre's products. The recipients' permission as set out in the Code was thus not required and no breach of the Code was ruled. Prescribing information was not required and thus a further ruling of no breach of the Code was ruled. There was no evidence that the representative had failed to maintain high standards and no breach of the Code was ruled.

An anonymous and non contactable complainant was concerned about the conduct of a representative from Pierre Fabre Ltd.

COMPLAINT

The complainant stated that it had been drawn to his/her attention by his/her peers that the representative in question had sent unsolicited emails to NHS colleagues over the last few months and did not have consent, documented or otherwise, to do this.

The emails, of which the complainant did not have copies but was sure that Pierre Fabre's records would validate, showed that the representative had discussed and asked to meet to help set up 'oral chemotherapy' clinics for use within clinicians' respective departments.

The complainant submitted that these emails were, and could be perceived as, promotional and no prescribing information was attached. The complainant asked if they had been formally certified for distribution and whether it could be confirmed that the representative had obtained permission from local oncology pharmacists to communicate with them via email.

The complainant stated that he/she was quite concerned that the pharmaceutical industry, and this representative in particular, appeared not to have been briefed specifically about the use of email; the Code was very clear about the potential issues regarding emailing customers, and stressed that it was completely inappropriate to mention company products in any email of this nature.

The complainant asked if the representative had recently undergone any refresher training on the Code that stressed the importance of certifying all promotional material.

When writing to Pierre Fabre the Authority asked it to consider Clauses 4.1, 9.9 and 15.2 of the Code.

RESPONSE

Pierre Fabre explained that it had investigated this matter and developed a process for the analysis and scrutinised all email traffic from this territory and considered that the allegations were unfounded.

Pierre Fabre did not send promotional material by email and so did not subscribe to any database of email addresses for health professionals. Any email address that the company used had been willingly provided by the recipient. Email communication was only with a very small number of specialised NHS staff.

Pierre Fabre stated that it had discussed this matter with the representative involved and agreed that it would print all email traffic to and from its central email server. This was scrutinised and analysed according to the core function of the primary recipient and with respect to the Code (especially Clauses 9.9, 4.1 and 15.2).

1 Clinical: consultants, specialist registrar (meeting notices from senior medical staff)
2 Pharmacy: specialist oncology pharmacists
3 Nurse: specialist nurses (chemotherapy, disease specialists (lung/breast cancer))
4 Other: managers, primary care trust (PCT) administrators and some representatives from other companies (shared meetings).

The analysis of email traffic could only be that which originated from the Pierre Fabre representative as, along with the complainant, it had little or no access to any subsequent communication cascade.

Six hundred and twenty one emails were reviewed of which 22% were in the relevant territory which was a large geographic area and the majority of the representative's work and email traffic (78%) was elsewhere. A breakdown of regional email traffic was provided.

As the complainant purported to be a pharmacist, Pierre Fabre had concentrated on describing email traffic with pharmacy although similar scrutiny was applied elsewhere. There were 24 emails to and from pharmacists and these were in 4 series. The usual length of each exchange was 5 emails. The long series in one city involved little input from the representative (mainly consultant/pharmacist within the hospital, copying in the representative). A further analysis of email sent to regional pharmacists was provided.

Pierre Fabre's office manager and managing director scrutinised the email content. The first email in each series had been studied for evidence that it might be unsolicited or promotional. A detailed breakdown was provided.

From the 4 email series, the first email referred to a specific earlier meeting and agreed action. The nature, content and duration of each exchange did not suggest that any were unsolicited (Clause 9) or used as promotional material requiring certification (Clause 4).

The representative in question had over 15 years' experience in the pharmaceutical industry spent mostly in a 'top 10' company and in oncology. This experience also included a period with management responsibilities, which included adherence to the Code by colleagues. The representative had passed the ABPI examination, was very familiar with the Code and adherence to both the letter and spirit of the Code was clearly demonstrated in all aspects of his/her work, conduct and communication.

Pierre Fabre's training included sessions on the Code adherence and all representatives received refresher training annually from an external agent. Pierre Fabre had no concerns regarding the awareness and understanding of the Code or the integrity of this very professional representative.

Pierre Fabre considered that it was very unfortunate that the complainant did not have any of the emails at issue and was unable to specify any detail other than help with oral chemotherapy clinics.

The subject of 'oral chemotherapy' was a part of a more general service re-design and modernisation programme and was an area of significant professional interest to the Department of Health (Quality, Innovation, Productivity and Prevention (QIPP), National Chemotherapy Advisory Group (NCAG), hospital trusts, commissioners and all professional bodies involved in the patient pathway (clinicians, nurses, managers and pharmacists)) and the privatisation of hospital outpatient pharmacy services. Other companies had also aligned their activities to support the NHS in this field. Given the opportunities for professional development within pharmacy, nursing and management associated with similar service re-design, Pierre Fabre highlighted that significant email traffic might be initiated and developed by NHS staff within each trust and without Pierre Fabre (or other company) involvement.

In response to a request for further information, Pierre Fabre explained that the matter had been discussed in detail with the representative involved. The analysis of the representative's external email traffic was for the whole territory in 2011 (to the date Pierre Fabre received the complaint) and the

omission of some areas was intended to streamline analysis and aid interpretation. Further details of email traffic in a greater regional area were provided.

Other areas of this territory (43% of email traffic) were outside the regions specified in the complaint. Pierre Fabre did not visit every hospital in the region.

Email was a preferred route of communication for most people in all aspects of business, including the pharmaceutical industry. The Code permitted email to be used for business and it was the responsibility of the industry to ensure that it was used appropriately.

The Code did not define 'non-promotional'. In its analysis, the content of each email was scrutinised to determine if it was 'promotional' to the point where it would require certification according to Clause 4, assessed to determine if the email complied with Clause 9.9 by looking for evidence to establish that there was an existing relationship or dialogue with the representative or company as a direct result of earlier meetings or discussions and compliant with Clauses 15.1 and 15.2 to demonstrate adequate knowledge of product and the standard of ethical conduct.

Pierre Fabre submitted that its representatives were strongly discouraged from using email to refer to any of the company's products by name (proprietary or non-proprietary), indications, dosages, costs, packs sizes or legal status, even when this might be permitted by the supplementary information to Clause 9.9. This fundamentally changed the nature of representative email and reduced the risk of email being used for promotion. With one exception, a clarification of a dose titration within an existing protocol (discussed below), none of the above information appeared in the representative's email and Pierre Fabre did not identify any email that required certification.

The exception mentioned above was one email in a sequence of two that contained a clarification of the recommended dose titration (a copy of the email was provided). This email exchange was with a pharmacist responsible for an established oral treatment service that obviously included, but was not limited to, a Pierre Fabre product. This was not considered to require certification and was considered to be compliant with Clause 15.1.

Two other references were made to 'oral chemotherapy clinics' in other email exchange series. Pierre Fabre highlighted that oral chemotherapy clinics were not a Pierre Fabre 'product' but a contemporary patient treatment pathway that required some re-alignment of medical, pharmacy, nursing and commissioning activity within the outpatient pathology/chemosuite/ pharmacy/hospital management to achieve. It was a management process within the hospital and although representatives from Pierre Fabre and other companies might be involved in some practical details, the responsibility and drive for this was universally down to the professional development of the health professionals and managers within the hospital trust.

Both email series that mentioned 'oral chemotherapy clinics' were included in this clarification submission. None included any product specific information (eg the name of Pierre Fabre's medicine) that would trigger the need for certification.

The first series mentioned an oral chemotherapy service that was already established within the hospital and included the use of several oral medicines (from different manufacturers and generics) and was not exclusive to Pierre Fabre. Pierre Fabre had previously provided patient briefing material to this clinic and this email communication explored the need to re-establish this service to the hospital. The aim of this exchange was to arrange an appointment between consenting adults and was successful.

The second series strongly suggested a pre-existing dialogue. The content did not include any information that would require formal certification as promotional material. The reference to an oral chemotherapy clinic was to highlight opportunities to observe professional developments that had already been made in an adjacent hospital.

As mentioned earlier, oral chemotherapy pathways were a management process and, given the multi-disciplinary nature of cancer treatment (doctor, nurse, pharmacist, manager), they could be hard to establish. When a centre had established this pathway, it was usually very proud of its achievements and often published or presented its experience and hosted visits from other centres. The above email exchange was considered to be the encouragement of inter-professional dialogue and was not considered to require certification.

Pierre Fabre did not distribute approved promotional material by email and did not subscribe to email directories or provide representatives with email addresses from proprietary listings. This removed an important risk of improper use of email. Any email addresses used by company representatives had been offered by the recipient to facilitate communication on matters of mutual interest, most usually relating to meetings, patient support (safety) items and appointments, ie acceptable electronic communication within the Code.

In the analysis conducted for the territory, Pierre Fabre was satisfied that the initial email was a direct result of an earlier meeting, a direct introduction from a hospital colleague and/or contained information that strongly suggested a pre-existing relationship with its representative or with the company (eg a support for an existing treatment service). Pierre Fabre did not find any evidence that any email might be unsolicited or unwelcome.

Cytotoxic chemotherapy for cancer treatment was associated with significant and potentially life threatening toxicity and its use was restricted to specialist centres only. Doses were calculated for each individual and support therapies were required before, during and after use of these products. It was essential that representatives were well trained

and it was satisfied that this individual was competent and proficient.

There was no evidence that email had been misused or abused. The only mention of product specific detail was a clarification of a dose escalation in an established protocol. This was appropriate and Pierre Fabre considered it had complied with Clauses 15.1 and 15.2.

Pierre Fabre stated that in its view it was strange that an 'anonymous' and uninvolved third party observer who did not have access nor was copied in on any of the electronic correspondence, despite the obvious ease with which this could be achieved, had complained. It also seemed strange that the complaint was based on a treatment delivery system that was already established in many NHS hospitals and included many products from different manufacturers and generics. Pierre Fabre noted that the NHS had rapidly privatised hospital outpatient pharmacies. This had created professional tensions between the few remaining NHS pharmacists in some hospitals and between other hospitals that had tried to retain their NHS based pharmacy systems. This tension was unrelated to the activity of a pharmaceutical representative from any company and it would be inappropriate for the industry to be targeted as a distraction from unrelated events. Given the nature of this complaint and the conduct of the complainant, Pierre Fabre considered that this was an important point for the PMCPA to consider.

In conclusion, Pierre Fabre hoped this additional information satisfied the Panel that Pierre Fabre upheld the spirit of the Code in its activities. Pierre Fabre considered that this complaint was not justified, was inappropriate and unfounded.

PANEL RULING

The Panel considered that the complaint solely concerned emails which referred to oral chemotherapy clinics. The Panel noted Pierre Fabre's submission that such clinics were not a company product or service but part of a re-designed patient treatment pathway which was the responsibility of, and driven by, individual hospital trusts. In that regard the Panel considered that the email series from October 2011 which did not refer directly or indirectly to oral chemotherapy clinics were not the subject of complaint.

Clause 9.9 stated, *inter alia*, that email must not be used for promotional purposes except with the prior permission of the recipient. The Panel noted Pierre Fabre's submission that it did not distribute promotional material by email and so did not subscribe to email directories or otherwise provide representatives with email addresses from proprietary listings. Any email address used had been willingly provided by the recipient to facilitate communication in relation to, *inter alia*, meetings and appointments. The Panel noted that the supplementary information to Clause 9.9 explained that an enquiry received by email could be responded to by email without specific permission; consent to do so being implied.

The Panel noted Pierre Fabre's submission that evidence of an existing relationship or dialogue with the representative or company as a direct result of previous meetings or discussion allowed it to assess compliance with Clause 9.9. In the Panel's view such factors did not determine whether the emails were promotional nor whether the requisite permission to send promotional emails was necessary and had been obtained. The Panel was concerned that the criteria used to determine whether representatives' email traffic was promotional were inadequate and lacking in detail.

The Panel examined the two sets of email traffic at issue. In the first series from July 2011 the representative sought a meeting to discuss potential company support for the oral chemotherapy service. There was a general reference to patient support packs. The Panel queried whether it was appropriate to refer albeit generally to patient support items in such an email. Such references might be seen as an inducement to gain an interview contrary to the provisions of Clause 15.3. However, no details were provided about the items and they were not the subject of complaint. There was no reference direct or indirect to Pierre Fabre's products. The second series of emails, dated July and October 2011, discussed a recent meeting where streamlining the patient pathway and best practice had been discussed. Again there was no reference to Pierre Fabre's products.

Whilst the Panel had some concerns about the emails it did not consider that either the first or second series were promotional on the narrow ground alleged. There was no reference direct or implied to Pierre Fabre's products. The recipients' permission as set out in Clause 9.9 was thus not required. No breach of Clause 9.9 was ruled. Prescribing information was not required and thus no breach of Clause 4.1 was ruled. There was no evidence that the representative had failed to maintain high standards. No breach of Clause 15.2 was ruled.

During its consideration of this case, and irrespective of its rulings above, the Panel was concerned about the company's submission on promotional content and representatives' emails. The company should always be mindful of the representative's promotional role and the impression given to health professionals in this regard.

Complaint received **3 November 2011**

Case completed **26 January 2012**

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

e-Promotion of Pradaxa

A general practitioner complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim on a third party website.

Pradaxa (75mg and 110mg) was indicated for primary prevention of venous thromboembolic events in adults who had undergone elective total hip or total knee replacement surgery. Pradaxa (110mg and 150mg) was indicated for the prevention of stroke and systemic embolism in certain adult patients.

The detailed response from Boehringer Ingelheim is given below.

The complainant noted that a clinical paper summary, 'Dabigatran versus warfarin in patients with atrial fibrillation', provided on the website, referred only to the relative risk in relation to the key efficacy outcomes for dabigatran 150mg/110mg vs warfarin. A breach of the Code was alleged.

The complainant further noted that the clinical summary provided hyperlinks to the reprints of the two papers by Connolly *et al* (2009 and 2010) that it was based upon. These reprints could be downloaded and printed; the complainant alleged that this promotional facility necessitated the provision of prescribing information and its omission was in breach of the Code.

The Panel noted that the supplementary information to the Code stated, inter alia, that relative risk should never be referred to without also referring to the absolute risk. Absolute risk could be referred to in isolation.

The Panel noted that a table of data in the clinical paper summary, inter alia, referred to the relative risk stroke or systemic embolism according to treatment group. The absolute rates were also stated thus the Panel ruled no breach of the Code.

The Panel noted that the page in question provided a prominent and direct link to the prescribing information. In the Panel's view this was the first part of the material. The hyperlinked publications were part of the same material and in that regard did not also need to include links to the prescribing information. The Panel considered that prescribing information had been provided as required. No breach of the Code was ruled.

The Panel considered that by providing hyperlinks to the two Connolly *et al* papers, Boehringer Ingelheim had, in effect, invited readers to access the publications. This was a solicited request not an unsolicited request as alleged and therefore no breach was ruled.

The complainant noted that on another page headlined Pradaxa for use in stroke prevention in atrial fibrillation as were the specifics of the licensed indication. The reader was not informed that this indication was restricted only to Pradaxa 150mg and 110mg and not 75mg which was also available but for a different indication. The complainant alleged that this was misleading by omission.

The complainant noted that again this page facilitated access to reprints and prescribing information had been omitted.

The Panel noted that the licensed dose for Pradaxa in the prevention of stroke and systemic embolism in patients with atrial fibrillation was 150mg twice daily reduced to 110mg twice daily in certain patients. Pradaxa 75mg was not licensed for this indication but could be used in the primary prevention of venous thrombotic events in elective total hip or knee replacement surgery. The Panel noted that the page in question did not refer to any dose of Pradaxa but, as in the above, provided a link to the prescribing information on a red band running across the top of the page. The Panel considered that reference to the 75mg dose on this page was not required, given that it related only to the use of Pradaxa in the prevention of stoke and atrial fibrillation. No breach of the Code was ruled.

The Panel noted that a subsection of the page at issue was headed 'Clinical paper summaries*' and below this were links to these summaries. The asterisk referred to a footnote which read 'Promotional information by Boehringer Ingelheim'. Clicking on the links opened up the clinical paper summaries from which the reader could click to access, inter alia, the prescribing information. The Panel noted, therefore, that the prescribing information was accessible not only from the first page but also from the hyperlinked pages. The requirement to provide prescribing information had been met and no breach of the Code was ruled.

The Panel noted its comments above with regard to the provision of solicited and unsolicited reprints and considered that they also applied here. No breach of the Code was ruled.

A general practitioner, complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim Limited on a third party website.

The complainant stated that he had no interest to declare other than to state that Boehringer Ingelheim's staff and activities had done little to improve the image of the UK pharmaceutical industry. However, his scrutiny of its activities had enhanced his understanding of the Code which was the only silver lining when it came to this clearly disreputable company.

Pradaxa (75mg and 110mg) was indicated for primary prevention of venous thromboembolic events in adults who had undergone elective total hip or total knee replacement surgery. Pradaxa (110mg and 150mg) was indicated for the prevention of stroke and systemic embolism in certain adult patients.

When writing to Boehringer Ingelheim, the Authority asked it to consider Clauses 4.1 and 7.2 of the Code. The Authority also noted that the provision of prescribing information with reprints was referred to in the supplementary information to Clause 10.1.

1 Reference to absolute risk and relative risk and the provision of prescribing information

COMPLAINT

The complainant referred to the provision of the clinical paper summary entitled 'Dabigatran versus warfarin in patients with atrial fibrillation' (ref DBG2430) and noted that the results presented in table 1 only reported the relative risk in relation to the key efficacy outcomes for dabigatran 150mg/110mg vs warfarin. The complainant alleged that the omission of the absolute risk values was in breach of the Code.

The complainant further noted that the clinical summary provided hyperlinks to the full paper reprints of the two papers by Connolly *et al* (2009 and 2010) that it was based upon. These reprints could be downloaded and printed; this promotional facility was organised by Boehringer Ingelheim with the aim of providing further promotional information about dabigatran. This therefore necessitated the provision of prescribing information which had been omitted in breach of the Code.

RESPONSE

Boehringer submitted that table 1 was based on the two publications, referred to in the clinical paper summary, by Connolly *et al* in which the absolute rates of stroke or systemic embolism were prominently given for the three treatment groups (dabigatran 110mg, dabigatran 150mg and warfarin) in the Randomized Evaluation of Long-Term Anti-coagulation Therapy (RE-LY) study. From table 1 it could be seen that these values were respectively 1.54%/year, 1.11%/year and 1.71%/year. The relative risk (95% confidence interval (CI)) and p values were also clearly presented in the table. The supplementary information to Clause 7.2 stipulated that relative risk should not be given without absolute risk as this could mislead the reader. In addition, table 1 was a faithful representation of the table as it appeared in the publication. Boehringer Ingelheim therefore firmly asserted that since the absolute rates were presented in table 1 alongside relative risk, there was no breach of Clause 7.2.

With regard to the hyperlink to the two papers by Connolly *et al*, Boehringer Ingelheim stated that this information was provided because it wanted the data relating to dabigatran to be readily available for prescribers to facilitate good understanding and good prescribing. The information was consistent with the summary of product characteristics (SPC) for Pradaxa and so Boehringer Ingelheim considered that the use of these papers was appropriate and complied with the Code.

Boehringer Ingelheim submitted that at the top of the page of the website there was a link to the prescribing information which was clearly prominent and positioned (reader's view) to the right hand side of the red banner. Boehringer Ingelheim therefore disagreed that prescribing information was not readily available for review by the reader. The supplementary information to Clause 10.1 stated that an unsolicited reprint of an article about a medicine should be accompanied by prescribing information. The hyperlink was found at the bottom of the page 'Connolly SJ, *et al*. Newly identified events in the RE-LY trial' N Engl J Med 2010;363:1875-1876.' Boehringer Ingelheim argued that in this instance the provision of the article was not unsolicited: on the website there was no indication nor promotion of the availability of reprints through downloading from the NEJM website; the reader must choose to click on the hyperlink without the knowledge of where or what they would be linked to; equally once on the NEJM website again the reader must choose whether or not to print the article. Given these factors Boehringer Ingelheim strongly believed that the article was not unsolicited (ie the reader had solicited it themselves) and so the provision of prescribing information for downloading was not required. Boehringer Ingelheim therefore strongly asserted that there was no breach of Clause 10.1.

The prescribing information was legible; linked and positioned prominently within the website and consistent with the SPC. Boehringer Ingelheim therefore asserted that there was no breach of Clause 4.1.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 stated that referring only to relative risk, especially with regard to risk reduction, could make a medicine appear more effective than it was. In order to assess the clinical impact of an outcome, the reader also needed to know the absolute risk involved. In that regard relative risk should never be referred to without also referring to the absolute risk. Absolute risk could be referred to in isolation.

The Panel noted that table 1 referred to the relative risk and p value of stroke or systemic embolism in patients treated with dabigatran 110mg vs warfarin (0.90; p=0.30) or dabigatran 150mg vs warfarin (0.65; p<0.001). The absolute rates (% patients/year) of stroke or systemic embolism in patients treated with dabigatran 110mg (1.54%/year), dabigatran 150mg (1.11%/year) or warfarin (1.71%/year) were also stated. In that regard the Panel considered that the requirements of Clause 7.2 in relation to relative and absolute risk had been satisfied. No breach of Clause 7.2 was ruled.

The Panel noted that the webpage in question promoted the use of Pradaxa for stroke prevention in atrial fibrillation. Running across the top of the page was a red band upon which the reader could click to access, inter alia, the prescribing information. The page also provided hyperlinks to the two Connolly *et al* publications. In that regard the Panel considered

that the publications themselves were part of the promotional campaign.

The Panel considered that the supplementary information to Clause 4.1, Electronic Journals, was relevant to the material before it. The supplementary information stated that the first part of an advertisement in an electronic journal, such as the banner, was often the only part of the advertisement that was seen by readers. It must therefore include a clear, prominent statement as to where the prescribing information could be found. This should be in the form of a direct link. The first part was often linked to other parts and in such circumstances the linked parts would be considered as one advertisement.

The Panel noted that the webpage in question provided a prominent and direct link to the prescribing information. In the Panel's view this was the first part of the material. The hyperlinked publications were part of the same material and in that regard did not also need to include links to the prescribing information. The Panel considered that prescribing information had been provided as required. No breach of Clause 4.1 was ruled.

The Panel noted that Clause 10.1 stated that reprints of articles in journals must not be provided unsolicited unless the articles had been refereed. The supplementary information to that clause stated that when providing an unsolicited reprint of an article about a medicine, it should be accompanied by prescribing information.

The Panel considered that by providing hyperlinks to the two Connolly *et al*, papers, Boehringer Ingelheim had, in effect, invited readers to access the publications. This was therefore a solicited request for the papers. In that regard the Panel did not consider that Clause 10.1 was relevant and so no breach of that clause was ruled.

2 Indication of licensed doses and the provision of prescribing information

COMPLAINT

The complainant referred to another page of the website (ref DBG2686) and noted that Pradaxa for use in stroke prevention in atrial fibrillation was headlined on this page as were the specifics of the licensed indication. The complainant further noted, however, that the reader was not informed that this indication was restricted only to Pradaxa 150mg and 110mg and not 75mg which was also available but for a different indication. The complainant alleged that this was misleading by omission.

The complainant noted that again this webpage facilitated access to reprints and as per point 1 above, prescribing information that should have been associated with, or accompanied, the reprints had been omitted.

RESPONSE

Boehringer Ingelheim noted that as Pradaxa 75mg was not licensed for stroke prevention in atrial fibrillation, to have provided the SPC for that medicine following a reference to stroke prevention in atrial fibrillation would have been inappropriate and confusing for the reader. Boehringer Ingelheim did not consider that it was misleading by omission not to refer to Pradaxa 75mg in this context. Boehringer Ingelheim proposed the opposite, namely that to refer to it here would be misleading. The complainant objected that the prescribing information was not available here but this was incorrect as it was available in the top right hand corner of the page, as before, in the form of a white on red hyperlink.

In summary Boehringer Ingelheim firmly asserted that there were no breaches of the Code in the materials referred to above and specifically no breaches of Clauses 4.1, 7.2 and 10.1.

Boehringer Ingelheim confirmed that it paid for the materials to be included on www.doctors.net.uk.

PANEL RULING

The Panel noted that the licensed dose for Pradaxa in the prevention of stroke and systemic embolism in patients with atrial fibrillation was 150mg twice daily reduced to 110mg twice daily in patients aged 80 years or over and patients with an increased risk of bleeding. Pradaxa 75mg was not licensed for this indication but could be used in the primary prevention of venous thrombotic events in elective total hip or knee replacement surgery. The Panel noted that the webpage in question did not refer to any dose of Pradaxa but, as in point 1 above, provided a link to the prescribing information on a red band running across the top of the page. The Panel noted that the title of the webpage was 'Pradaxa – stroke prevention in atrial fibrillation'. The Panel considered that reference to the 75mg dose on this webpage was not required, given that it related only to the use of Pradaxa in the prevention of stoke and atrial fibrillation. The Panel did not consider that the webpage was misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that a subsection of the page at issue was headed 'Clinical paper summaries*' and below this were links to these summaries. The asterisk referred to a footnote which read 'Promotional information by Boehringer Ingelheim'. Clicking on the links opened up the clinical paper summaries. Running across the top of each summary was the same red band as before upon which the reader could click to access, *inter alia*, the prescribing information. The Panel noted, therefore, that the prescribing information was accessible not only from the first page but also from the hyperlinked pages. The Panel considered that the requirement to provide prescribing information had been met. No breach of Clause 4.1 was ruled.

The Panel noted its comments above with regard to Clause 10.1 and considered that they also applied here. No breach of Clause 10.1 was ruled.

Complaint received **15 November 2011**

Case completed **2 February 2012**

ANONYMOUS V ASTRAZENECA

Conduct of representative

An anonymous complainant who described him/herself as a very disappointed practice manager questioned the integrity of a representative from AstraZeneca. The complainant alleged that the representative was rude, ill mannered and completely unprofessional and had no respect for the doctors' and nurses' busy time schedules. The representative was late for meetings and had given out diaries with dates already pencilled in on the days when he/she wanted to arrange both appointments and lunch meetings for the surgeries. Further the representative constantly put people in very uncomfortable situations; he/she intimidated receptionists by not taking 'No' for an answer and waited for the doctors in the car park to talk to them as they left the surgery. Last week the representative had talked to a doctor in the car park about a medicine for type 2 diabetes that the doctor had not heard about and which he subsequently discovered was not even licensed in the UK.

The detailed response from AstraZeneca is given below.

The Panel noted that the complainant was anonymous and non-contactable. The PMCPA's Constitution and Procedure stated that it was for complainants to prove their complaints on the balance of probabilities. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties. The Panel noted that the complainant had provided no evidence to support the allegations.

The Panel noted AstraZeneca's acknowledgement that the representative's manner was regarded as slightly eccentric by some people and that it evoked various responses from health professionals. The Panel noted the complainant's broad allegations that the representative was rude, ill-mannered and intimidated receptionists. The Panel noted that often in cases concerning what a representative had said or done, the company's response was sent to the complainant for comment before the Panel made its ruling. This was not possible when the complainant was anonymous and had provided no contact details. It was thus impossible in this case to determine what had transpired between the representative and any of his/her contacts.

With regard to punctuality, the company's investigation revealed that, at some point in the past, the representative had been late for meetings due to earlier meetings over running. Although health professionals had not complained, the matter was addressed at the time by the representative's manager.

The Panel noted that the representative denied holding conversations with health professionals in car parks and that AstraZeneca had found no evidence to support the allegation. The Panel noted that it was not possible to contact the complainant for more details.

The Panel noted that the Code required representatives, *inter alia*, to maintain a high standard of ethical conduct in the discharge of their duties and to ensure that the frequency, timing and duration of calls together with the manner in which they were made did not cause inconvenience. The Panel noted that whilst there had been some concerns in the past about the representative's punctuality it was not a breach of the Code *per se* to be late for a meeting. The Panel noted that the complainant's allegation in this regard was non-specific with no details about the circumstances.

The Panel considered that the complainant had submitted no evidence to establish that on the balance of probabilities any aspect of the representative's conduct was such as to be in breach of the Code as alleged and the Panel thus ruled no breaches of the Code.

The Panel noted that AstraZeneca had not produced any 2011 or 2012 diaries for distribution to health professionals and that such distribution was denied by the representative. The Panel noted that there was no evidence to support the provision of diaries as alleged and thus it ruled no breach of the Code.

With regard to the promotion of an unlicensed medicine, the Panel noted AstraZeneca's submission that it had a zero tolerance attitude to such behaviour. The company submitted that its employees were well briefed on this point and all were tested on their understanding of relevant policy documents. The representative had denied promoting an unlicensed medicine and AstraZeneca had found no evidence to the contrary. The Panel considered that there was no evidence to support the allegation and it thus ruled no breach of the Code.

The Panel noted its rulings above and considered that AstraZeneca had not failed to maintain high standards and ruled no breach of the Code on this point and consequently ruled no breach of Clause 2.

The Authority received an anonymous complaint from a very disappointed practice manager about the conduct of an AstraZeneca UK Limited representative.

COMPLAINT

The complainant stated that it was to his/her great regret that he/she was complaining but considered that under the circumstances his/her action was justified.

The complainant questioned the integrity of the representative. The complainant alleged that the representative was rude, ill mannered and completely unprofessional and had no respect for the doctors' and nurses' busy time schedules. The representative was late for meetings and had recently given out diaries with dates already pencilled in on the days when he/she wanted to arrange both appointments and lunch meetings for the surgeries. The complainant had been advised by representatives from different companies that representatives were no longer allowed to give out diaries, pens and post-its and it was very apparent that this representative had no respect for the rules and regulations. The complainant alleged that the representative in question constantly put people in very uncomfortable situations; he/she intimidated receptionists by not taking 'No' for an answer and waited for the doctors in the car park to talk to them as they left the surgery. Last week the representative waited by one doctor's car and during their conversation mentioned a medicine for type 2 diabetes that the doctor had not heard about; when he returned to the surgery he was surprised to find that the medicine was not even licensed in the UK.

The complainant stated that the practice had always found AstraZeneca to be one of the best pharmaceutical companies with the most knowledgeable and professional representatives in the area and was saddened to have to submit this complaint.

When writing to AstraZeneca, the Authority asked it to consider Clauses 3.1, 15.2, 15.4, 15.9, 18.1, 9.1 and 2 of the Code.

RESPONSE

AstraZeneca stated that it undertook a full investigation into this complaint and had interviewed the representative, past and present managers, other colleagues in AstraZeneca and its partners and health professionals.

AstraZeneca stated that it had not been able to uncover any evidence to support the allegation that the representative lacked professionalism, that he/she was rude, ill-mannered, did not respect health professional's busy time schedules, was late for meetings, intimidated reception staff and waited to talk with doctors in car parks. What was clear was that, *inter alia*, a personality described as slightly eccentric resulted in a varied health professional response to the representative. Managers had been aware of this, had coached the representative appropriately and were confident that the representative had never failed to respect a clinician's time. The managers reported that they had never witnessed overtly negative responses from customers; on the contrary it had been acknowledged that many customers that 'loved' the representative and found him/her very supportive and professional, including some who refused to see other representatives.

During his/her career as an AstraZeneca medical representative, the company was aware of a single self-reported misunderstanding with a practice manager in relation to what the practice believed was allowed under the Code (lunch was requested without an opportunity for an educational presentation), resulting in the representative not being able to secure an appointment for a promotional call. This was corroborated by the representative's manager. Equally the managers had not witnessed intimidating behaviour towards reception staff.

In the past a manager had noticed that the representative was late for meetings, due to previous meetings over-running; this was addressed at the time by the manager. From the information collated during the course of the investigation, it appeared that no health professionals or administrative staff had complained directly to the representative about punctuality or to his/her manager or to AstraZeneca. The representative denied having car park conversations and none of the health professionals interviewed felt that the representative had stalked them.

AstraZeneca submitted that there was no evidence to support the allegation that the representative distributed diaries with dates for meetings pencilled in. AstraZeneca was one of the first pharmaceutical companies to stop distributing promotional aids and gifts, predating changes to the Code in this regard. AstraZeneca had not produced any 2011 or 2012 diaries for distribution to health professionals. The representative displayed clear awareness that this was not allowed and denied distributing diaries, including any that could have been self-purchased. The representative confirmed that he/she had entered proposed meeting dates into some practice diaries, but only upon request by the practice administrative staff; this was not an uncommon practice.

In the absence of details from the complainant, AstraZeneca stated that it had not been possible to establish any evidence to support the alleged promotion of a medicine prior to the grant of marketing authorization. The representative refuted the allegation of promoting any unlicensed medicine and at interview managers did not express any concern that off-label promotion had taken place.

All AstraZeneca employees had been fully briefed on the requirement not to promote medicines outside of their licensed indication or prior to the grant of a marketing authorization and were also in no doubt that failure to adhere to these principles would be met with the most severe sanctions as AstraZeneca adopted a zero tolerance position in this regard. All AstraZeneca personnel were expected to read the relevant policy document and to undertake an e-learning module which included a test of understanding. At the end of the process employees had to confirm that they understood the content of the policy and they agreed to abide by it. The representative had done this recently and had also passed the ABPI Medical Representatives Examination some years ago.

No AstraZeneca sales team had been briefed on medicines in development. In addition, there were

clear processes in place for referral to the medical team of any queries that might relate to unlicensed medicines, including validation of requests by the medical team to ensure that the response was tailored to the specific requirement of the health professional. This external validation step had not identified an issue with the appropriateness of the representative's referrals to the medical team. It had also been confirmed that the representative had not actively sought information from the medical team in relation to unlicensed medicines.

AstraZeneca submitted that the lack of specific information/detail made it difficult to establish with absolute certainty that there was or was not a case to be made for conduct unbecoming of a medical representative. In summary, AstraZeneca maintained that its representatives, including the representative at issue, had been suitably trained and briefed to conduct themselves in a professional manner at all times. Representatives had also been rigorously educated on the requirement not to engage in off-label promotion and strongly advised of the personal consequences of not adhering to this requirement.

In the absence of evidence to support any of the allegations, AstraZeneca denied a breach of Clauses 15.2, 15.4, 15.9, 18.1 and 3.1 (and consequently no breach of Clauses 9.1 and 2).

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The introduction to the PMCPA Constitution and Procedure stated that it was for complainants to prove their complaints on the balance of probabilities. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties. The Panel noted that the complainant had provided no evidence to support the allegations.

The Panel noted AstraZeneca's acknowledgement that the representative's manner was regarded as slightly eccentric by some people and that it evoked a varied health professional response to him/her. The Panel noted the complainant's broad allegations that the representative was rude, ill-mannered and intimidated receptionists. The Panel noted that often in cases concerning what a representative had said or done, the company's response was sent to the complainant for comment before the Panel made its ruling. This was not possible when the complainant was anonymous and had provided no contact details. It was thus impossible in this case to determine what had transpired between the representative and any of his/her contacts.

With regard to punctuality, the company's investigation revealed that, at some point in the past, the representative had been late for meetings due to earlier meetings over running. Although health professionals had not complained, the matter was addressed at the time by the representative's manager.

The Panel noted that the representative denied holding conversations with health professionals in car parks and that AstraZeneca had submitted that none of the heath professionals it had interviewed had felt that the representative had stalked them. The Panel noted that it was not possible to contact the complainant for more details.

The Panel noted that the Code required representatives, *inter alia*, to maintain a high standard of ethical conduct in the discharge of their duties (Clause 15.2) and to ensure that the frequency, timing and duration of calls together with the manner in which they were made did not cause inconvenience (Clause 15.4). The Panel noted that whilst there had been some concerns in the past about the representative's punctuality it was not a breach of the Code *per se* to be late for a meeting; the supplementary information to Clause 15.4 stated that if, for unavoidable reasons, an appointment could not be kept, the longest possible notice must be given. The Panel noted that the complainant's allegation in this regard was non-specific with no details about the circumstances.

The Panel considered that the complainant had submitted no evidence to establish that on the balance of probabilities any aspect of the representative's conduct was such as to be in breach of the Code as alleged. The Panel thus ruled no breach of Clauses 15.2 and 15.4.

The Panel noted that AstraZeneca had not produced any 2011 or 2012 diaries for distribution to health professionals and that such distribution was denied by the representative. The representative acknowledged that, on request by practice staff, he/she had entered proposed meeting dates into some practice diaries. The Panel queried whether such conduct was acceptable even when requested by practice staff. There was however no complaint on this point. The Panel noted that there was no evidence to support the provision of diaries as alleged and thus ruled no breach of Clause 18.1.

With regard to the promotion of an unlicensed medicine, the Panel noted AstraZeneca's submission that it had a zero tolerance attitude to such behaviour. The company submitted that its employees were well briefed on this point and had all had to read the relevant policy document and be tested on their understanding of it. The representative had denied promoting an unlicensed medicine and AstraZeneca had found no evidence to the contrary. The Panel considered that there was no evidence to support the allegation and thus ruled no breach of Clauses 3.1 and 15.9.

The Panel noted its rulings above and considered that AstraZeneca had not failed to maintain high standards and thus ruled no breach of Clause 9.1 and consequently ruled no breach of Clause 2.

Complaint received **2 December 2011**

Case completed **5 January 2011**

MEDA v ALK-ABELLÓ

Jext website

Meda Pharmaceuticals complained about ALK-Abelló's website (www.jext.co.uk) which provided health professionals and patients with information about anaphylaxis and its medicine, Jext (adrenaline tartrate auto-injector). Jext was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) to insect stings, foods, medicines and other allergens as well as idiopathic or exercise induced anaphylaxis. Meda also supplied an adrenaline auto-injector (EpiPen) for allergic emergencies.

Meda alleged that ALK-Abelló had not provided complete and accurate instructions for use of the device in breach of the Code; it had not accurately reflected the marketing authorization. Meda submitted that this was critically important as patients might have less than ten minutes to administer adrenaline in the event of an anaphylactic reaction. In addition, adrenaline auto-injectors were single use devices and if administered incorrectly, there was no second chance. Therefore the user must be trained and confident in the correct use.

Specifically, the Jext website had the method of administration presented as a series of images on both the patient and health professional sections. These images were reproduced from the summary of product characteristics (SPC) and the patient information leaflet (PIL). Image number 3 from Section 6.5 of the SPC and its accompanying text 'Place the black injector tip against your outer thigh, holding the injector at a right angle (approx. 90°) to the thigh' was absent from the instructions on both sections of the website.

The detailed response from ALK-Abelló is given below.

The Panel noted that Jext was indicated for use in the emergency treatment of severe, acute allergic reactions (anaphylaxis). It was critically important that patients knew exactly how to use the Jext auto-injector correctly. It was a single-use device and once activated could not be used again.

The website at issue included a page headed 'How does Jext work?' which illustrated, in a number of diagrams, how to use the device. The first four of these diagrams were the same as diagrams 1, 2, 4 and 5 of the SPC. The third diagram included in the SPC, but omitted from the website, depicted the Jext device held against the thigh with the 90° angle labeled. The third diagram on the website, however, clearly showed the device being held against the thigh at the correct angle. In the Panel's view the 90° angle was clearly illustrated albeit not labeled. In addition to the static diagrams on the website, patients could access a video via the same page of the website which demonstrated how to use Jext. In the Panel's view, the instructions for use on the website were not inconsistent with the particulars listed in the Jext SPC. No breach of the Code was ruled.

Meda Pharmaceuticals Limited complained about ALK-Abelló Ltd's website (www.jext.co.uk ref 552AD) which provided health professionals and patients with information about anaphylaxis and its medicine Jext (adrenaline tartrate auto-injector). Jext was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) to insect stings, foods, medicines and other allergens as well as idiopathic or exercise induced anaphylaxis. Meda also supplied an adrenaline auto-injector (EpiPen) for allergic emergencies.

COMPLAINT

Meda stated that Jext was launched in the UK in September 2011. The website at issue was a resource for patients and health professionals to receive information on the correct use of Jext. Meda alleged that ALK-Abelló had not provided complete and accurate instructions for use of the device in breach of Clause 3.2; it had not accurately reflected the marketing authorization.

Meda submitted that this was critically important due to the nature of the condition being treated. Evidence showed that patients might have less than ten minutes to administer adrenaline in the event of an anaphylactic reaction, depending on the allergen. In addition, adrenaline auto-injectors were single use devices, meaning that if they were administered incorrectly, there was no second chance. Therefore the user must be trained and confident in the correct use. This was especially relevant for a user who has been previously trained on a different auto-injector. Meda considered that ALK-Abelló had attempted to present Jext as identical to the current standard of care by deliberately omitting a step in the instructions for use.

Specifically, the Jext website had the method of administration presented as a series of images on both the patient and health professional sections. These images were reproduced from the summary of product characteristics (SPC) and the patient information leaflet (PIL). Image number 3 from Section 6.5 of the SPC and its accompanying text 'Place the black injector tip against your outer thigh, holding the injector at a right angle (approx. 90°) to the thigh' was absent from the instructions on both sections of the website.

Jext was administered differently from other adrenaline auto-injectors on the UK market. Meda considered that as a newly launched product with which patients and prescribers were unfamiliar, it

was even more important that they were presented with accurate and consistent information. Meda stated that the EpiPen auto-injector was the current standard of care and had been on the UK market for over 15 years. It was administered by a so called 'swing and jab' technique, where the device was held away from the outer thigh and positively jabbed against the leg to trigger the injection mechanism. In contrast, Jext used a 'place and press' method, whereby the device must be placed onto the leg and when in place, pressure applied to trigger the injection. Meda alleged that by excluding the description of the 'place' step in the instructions for use, ALK-Abelló might have placed users at risk of incorrect administration of the device. Worse, users might believe that they could administer Jext in the same way as they would an EpiPen auto-injector and that the devices were interchangeable.

Meda submitted that EpiPen auto-injectors were well established in the UK with a market share of over 95%. Therefore patients, prescribers, pharmacists and other stakeholders were versed in the method of administration. Meda further submitted that if a patient used the 'swing and jab' technique with Jext, the device might malfunction. Such errors in use could be catastrophic for a patient suffering from anaphylaxis. Meda therefore considered that it was vital that the complete instructions were displayed in educational and promotional materials. The website in question was both educational and promotional.

Since first contacting ALK-Abelló about this matter in September 2011, Meda had observed that other materials issued by ALK-Abelló contained the same set of incomplete instructions, for example a pad of instruction sheets for pharmacists to pass to patients (ref 593bAD). From a patient's perspective, it could be confusing to find that the instructions in the pack differed from those on the website and the leaflet provided by the pharmacist, which further highlighted the problem. Further examples were the quotations 'It's similar to your EpiPen, so you don't need any re-training' and 'if you're moving from your EpiPen, you use it in the same way.' Meda noted that although these statements were on an international Jext website (in English) and not part of this complaint, they helped to illustrate the company's concern.

Meda submitted that unfortunately inter-company dialogue had failed to resolve this matter. Meda had previously alleged that a Jext leavepiece was in breach of Clause 3.2 (Case AUTH/2405/5/11) and other clauses. In that case the PMCPA ruled there was no breach and part of the justification for the incomplete instructions for use was that the leavepiece was not part of the patient training support programme for Jext. In the present case, the instructions for use presented on the Jext website were explicitly for the support of patients and health professionals, in addition to being promotional. Meda therefore repeated its allegation that the website was in breach of Clause 3.2 and represented a potential risk to patient safety. The complete instructions for use of Jext should be consistently displayed on this and all other materials issued by ALK-Abelló.

RESPONSE

ALK-Abelló stated that Jext was an adrenaline auto-injector indicated for emergency self-administration of adrenaline to treat anaphylaxis. The Jext website was designed to be a resource for patients prescribed Jext with a separate section for health professionals treating patients with severe allergy. The website contained both graphic and audio-visual elements designed to instruct patients in the correct use of Jext in a potentially life threatening situation. These instructions for use were developed in conjunction with senior health professionals in the field of allergy and also with a patient organisation which represented patients living with severe allergy. The instructions for use were designed to be informative, concise and easily understood by the widest range of patients possible.

The instructions for use of Jext as shown on the website featured diagrams based on those in the SPC which had been simplified by removing one redundant diagram which specified that the device must be held at a 90° angle. The location of injection and 90° angle were clearly demonstrated in the subsequent diagram. The instructions on the website were further enhanced by an additional two diagrams advising the patient to call 999 and when to administer a second injection if required. ALK-Abelló believed the instructions for use of Jext as shown on the website were consistent with those in the SPC and the PIL. In Case AUTH/2405/5/11 the Panel ruled that the requirement to place the black tip of the Jext against the outer thigh at a 90° angle was clear in diagram number four in the SPC.

ALK-Abelló refuted the allegation that omitting diagram three was an attempt to present Jext as identical to EpiPen which required swinging from a distance of 10cm away from the thigh to activate the injection.

Directly below the instructions for use, in the same window on the website, was a direct link to a patient video which clearly demonstrated the correct administration technique with the recommendation 'To ensure that you, your family, friend and colleagues know how to administer your Jext, watch the comprehensive demonstration video.' A copy of this video was provided.

ALK-Abelló was concerned that Meda had complained directly to the PMCPA without inter-company dialogue or supporting data. Meda's statement about the possible malfunction of the Jext device was completely unfounded. ALK-Abelló submitted that Meda had deliberately abused the PMCPA system in an attempt to have published unfounded allegations denigrating Jext which could not be used in promotional literature without breaching the Code. ALK-Abelló therefore respectfully requested that Meda provide to both the PMCPA and ALK-Abelló robust data to substantiate these allegations or withdraw them unreservedly.

ALK-Abelló had provided Meda with details of the international website as part of a separate inter-

company dialogue on 26 September. Meda had acknowledged that this website was outside the scope of the Code. ALK-Abelló had received no further correspondence on this matter. ALK-Abelló believed therefore it was inappropriate for Meda to refer to this non-UK website in this complaint.

Both ALK-Abelló and Meda acknowledged that it was acceptable within the Code to be consistent with the particulars as listed in the SPC without reproducing verbatim those particulars, thus adhering to Clause 3.2.

Meda had requested that the Panel make a ruling that the complete instructions for use of Jext be consistently displayed on the website and all other materials issued by ALK-Abelló. Patient support and educational materials needed to be appropriate for the intended audience and might take different forms. Due to the range of patients prescribed adrenaline auto-injectors a one-size-fits-all approach was not appropriate, as such ALK-Abelló produced bespoke patient support and educational materials specific to different groups and based on recommendations of patient support groups and national allergy specialists. ALK-Abelló suggested that it was inappropriate to mandate how instructions for use were displayed, rather they should comply with Clause 3.2 in the most appropriate form for the intended audience.

ALK-Abelló took very seriously its commitment to abide by the Code and believed that the Jext instructions for use were fully consistent with the SPC and not in breach Clause 3.2.

PANEL RULING

The Panel noted that although ALK-Abelló had submitted that there had been a lack of inter-company dialogue, correspondence provided by Meda showed that the two companies had discussed, to some extent, the matter at issue. It appeared, however, that the complaint to the Authority raised some aspects of patient safety which had not previously been discussed with ALK-Abelló. Meda had, however, only alleged a breach of Clause 3.2 of the Code and so the Panel only considered this aspect of the complaint.

The Panel noted that Jext was indicated for use in the emergency treatment of severe, acute allergic reactions (anaphylaxis). It was critically important that patients knew exactly how to use the Jext auto-injector correctly. It was a single-use device and once activated could not be used again.

The website at issue included a page headed 'How does Jext work?' which illustrated, in a number of diagrams, how to use the device. The first four of these diagrams were the same as diagrams 1, 2, 4 and 5 of the SPC. The third diagram included in the SPC, but omitted from the website, depicted the Jext device held against the thigh with the 90° angle labeled. The third diagram on the website, however, clearly showed the device being held against the thigh at the correct angle. In the Panel's view the 90° angle was clearly illustrated albeit not labeled. In addition to the static diagrams on the website, patients could access a video via the same page of the website which demonstrated how to use Jext. In the Panel's view, the instructions for use on the website were not inconsistent with the particulars listed in the Jext SPC. No breach of Clause 3.2 was ruled.

Complaint received **6 December 2011**

Case completed **5 January 2012**

HEALTHCARE JOURNALIST v NOVARTIS

Galvus press release

A journalist from a pharmaceutical trade magazine complained about a Galvus (vildagliptin) press release from Novartis Pharma AG which detailed the approval in the EU of Galvus for type 2 diabetes patients with moderate or severe renal impairment with limited treatment options.

The complainant noted the claim 'Controlling blood sugar levels in patients with type 2 diabetes and renal impairment can be complex as many oral anti-diabetic medicines are not recommended for use, are contraindicated or should be used with caution. As a result, physicians have few treatment options for these high-risk patients' and alleged that the whole press release was tailored to meet the view that there were 'few treatment options' for type 2 diabetics with renal impairment, which was not so. There were already two other medicines with licences for this indication and whilst the complainant did not expect Novartis to name its competitors, to imply they did not exist was not correct.

The complainant further alleged that Cavanaugh (2007), cited in the press release, which stated that there were indeed few treatment options for this patient population was no longer correct; an out-of-date study had been used to back up a false assertion.

The detailed response from Novartis is given below.

The Panel noted the submission from Novartis UK that it had had no part in the creation, review or distribution of the press release which was issued by Novartis Pharma AG based in Switzerland. The circulation list provided, however, showed that the press release was sent mainly to UK-based publishers including a number of UK-specific publications such as the BMJ.

The supplementary information to the Code required that activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities took place or the materials were used. The press release was issued by a company based in Switzerland but insomuch as it was sent to specific UK publications, the Panel considered that that aspect of its use came within the scope of the Code.

The press release was entitled 'Novartis drug Galvus approved in EU for type 2 diabetes patients with moderate or severe renal impairment with limited treatment options'. Underneath the title were two bullet points; the first referred to the percentage of patients with type 2 diabetes affected by renal impairment (25%) and the second stated 'Majority of currently available medications are not recommended, contraindicated or have to be taken with caution in this population'. The press release went on to state that the approval of Galvus for use in this patient population 'expands treatment options for patients with moderate or severe renal impairment'. A Novartis employee from the global company was quoted as stating that the approval provided physicians with a '…much-needed new treatment to control blood sugar in a vulnerable patient population…'.

The Panel noted Novartis's submission that of 19 medicines available to treat type 2 diabetes (not including insulin), only three were indicated without the need for caution in both moderate or severe renal impairment. Two products were mentioned by the complainant. Onglyza could only be used at a lower dose and in severe renal impairment with an additional advisory caution. Trajenta could be used without caution or dose adjustment in severe renal failure. Galvus required a dose adjustment in moderate or severe renal impairment or with end stage renal disease when the recommended dose was 50mg once daily.

The Panel noted the statement quoted by the complainant from the press release 'Controlling blood sugar levels in patients with type 2 diabetes and renal impairment can be complex as many oral anti-diabetic medicines are not recommended for use, are contraindicated or should be used with caution'. Given that the title of the press release referred to '…limited treatment options', the text referred to 'few treatment options' and 'expanding treatment options', the Panel did not consider that the press release conveyed that Galvus had 'plugged a gap in the market' as alleged. It was clear from the press release that there were already 'a few' treatment options available and that Galvus had added to these. No breach of the Code was ruled.

The Panel noted that since Cavanaugh had been published, at least two medicines (Onglyza and Trajenta) and Galvus had been approved for use in type 2 diabetes with renal impairment. It might be argued that this was not the impression given by the use of a 2007 reference. On balance, however, the Panel considered that it was still the case that treatment options were limited as stated in the paper. No breaches of the Code were ruled including no breach of Clause 2.

A healthcare journalist with a pharmaceutical trade magazine complained about a press release about Galvus (vildagliptin) which he had received by email from Novartis Pharma AG. Galvus was indicated for the treatment of type 2 diabetes mellitus as dual oral therapy in combination with metformin, a sulphonylurea or a thiazolidinedione. The press

release was about the approval in the EU of Galvus for type 2 diabetes patients with moderate or severe renal impairment with limited treatment options.

COMPLAINT

The complainant noted the claim 'Controlling blood sugar levels in patients with type 2 diabetes and renal impairment can be complex as many oral anti-diabetic medicines are not recommended for use, are contraindicated or should be used with caution. As a result, physicians have few treatment options for these high-risk patients' and stated that the whole press release was tailored to meet the view that there were 'few treatment options' for type 2 diabetics with renal impairment which was not so. Several months ago the European Medicines Agency (EMA) approved Boehringer Ingelheim's Trajenta (linagliptin) for this indication and AstraZeneca/Bristol-Myers-Squibb's Onglyza (saxagliptin) gained an extended European licence for this indication in March.

The complainant alleged that essentially, Novartis wanted to convey that it had plugged a gap in a market, but it had simply added to two already available medicines in Europe for the licence it had gained. Novartis had been deliberately underhand. The complainant did not expect Novartis to name its competitors but to imply they did not exist was not correct.

The complainant also questioned a reference in the press release as a point of corroboration. The third reference cited (Cavanaugh 2007) stated that there were indeed few treatment options for this patient population but this was no longer correct. The complainant alleged that Novartis had deliberately used an out-of-date study to back up its false assertion.

The complainant submitted that so underhand was it that a competitor magazine had printed the story as fact and stated that there were few other treatments and went with the angle that Galvus had plugged a gap in the market.

When writing to Novartis, the Authority asked it to respond in relation to the requirements of Clauses 7.2, 22.2 and 2 of the Code.

RESPONSE

Novartis stated that the press release was created, reviewed and distributed by its global colleagues at Novartis Pharma AG based in Basel, Switzerland. As Novartis UK had no part in the creation, review or distribution of it, it had not been approved under the UK Code as this was not applicable.

After approval by the global compliance team, the press release was sent by its medical media agency to a list of international medical publications which it compiled as directed by the global Novartis organization. A copy of the circulation list was provided. Novartis submitted that this demonstrated that this was a general listing for European and international publications.

During the course of discussions with other reporters in the publishing house regarding this press release, it was recommended to the medical media agency that a particular individual would be the appropriate contact and thus the press release was emailed directly to him by the medical media agency. Subscriptions for the trade magazine were available via the online site.

The Authority specifically raised the question of amendments to the press release by Novartis to include reference to existing treatments and asked for information on this matter. The complainant's related statement was slightly ambiguous, and therefore Novartis answered the Authority's specific question: Novartis UK's global colleagues confirmed that no amended press release was issued. However, it appeared to Novartis UK that the complainant had referred to the coverage by a competitor publication, and that this publication took it upon itself to subsequently amend its story to include existing treatments within the same class.

Novartis noted that the complaint related to the following statement:

> 'Controlling blood sugar levels in patients with type 2 diabetes and renal impairment can be complex as many oral anti-diabetic medicines are not recommended for use, are contraindicated or should be used with caution. As a result, physicians have few treatment options for these high-risk patients.'

The complainant alleged that this statement and Cavanaugh to which it referred were used to endorse the view that treatment options were 'limited' which could not be substantiated.

Cavanaugh was a comprehensive review of the issues for diabetes management in patients with chronic kidney disease and reviewed the treatment options available. It considered which medicines could be used with no dose adjustment, where dose adjustment was required or whether the medicine was to be used with caution and finally whether it was contraindicated in this patient population and so should be avoided. Novartis believed that despite the article being published in 2007 treatment options for patients with chronic kidney disease had not materially changed.

Novartis noted that the complainant had submitted that the availability of two newer gliptins (Onglyza and Trajenta; the former with a licence amendment in 2011 and the latter newly launched in 2011), made the claim incapable of substantiation as it was therefore not balanced or based on an up-to-date evaluation of all the evidence.

Novartis noted that the Electronic Medicines Compendium website (www.medicines.org.uk) listed 19 medicines available in the UK (either as single agent therapy or combination therapy) for the treatment of type 2 diabetes; only three were indicated without the need for caution in both moderate or severe renal impairment in the diabetic

patient population which the press release specifically addressed. All the others were either contraindicated, not recommended or to be used with caution (this list did not include insulin preparations). Even the licence details of the two gliptins mentioned by the complainant were such that Onglyza could be used at the lower dose in moderate renal impairment but for patients with severe renal impairment at a lower dose with an advisory caution, whilst Trajenta could be used without caution or dose adjustment.

Therefore the statement that the majority of currently available medications were either not recommended, contraindicated or had to be taken with caution in this population remained true, even when including the two gliptins noted by the complainant.

With regard to Clauses 22.2 and 2 Novartis submitted that, as demonstrated by the circulation list the press release was issued to the healthcare industry press. The target audience was journalists familiar with this type of press release and/or health professional experts in the therapy area who would be familiar with the treatment options in renally impaired diabetics.

Novartis considered that the press release presented newsworthy information for the additional European licence approval for Galvus. The content of the press release was not an unqualified claim for Galvus as the only treatment in this patient group but highlighted that it was an additional choice where treatment choices were limited.

In keeping with the requirements of Clause 22.2 Novartis therefore considered this press release was factual and presented in a balanced way. Novartis did not consider it raised unfounded hopes of a treatment in this patient population or that it was misleading with respect to the safety of the product.

Novartis submitted that, furthermore, the press release did not contain statements which would encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. Therefore, Novartis did not consider that the press release warranted breaches of Clauses 7.2 and 22.2 or that Novartis had failed to maintain high standards or brought discredit to, or reduced confidence in, the pharmaceutical industry warranting a breach of Clause 2.

PANEL RULING

The Panel noted the submission from Novartis that it had had no part in the creation, review or distribution of the press release in question, and that it was issued by Novartis Pharma AG based in Basel, Switzerland. The Panel noted from Novartis's submission that the press release was sent to 'international medical publications'. According to the circulation list provided, however, the press release was sent mainly to publishers based in the UK including a number of UK-specific publications such as The Pharmaceutical Journal, BMJ and the on-line BBC Health News.

The supplementary information to Clause 1.8, Applicability of Codes, required that activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities took place or the materials were used. The press release in question was issued from a company based in Switzerland but insomuch as it was sent to specific UK publications, the Panel considered that that aspect of its use came within the scope of the Code. The Panel noted the advice in the supplementary information to Clause 14.3, Examination of Other Material, that material which related to medicines but which was not intended as promotional material for those medicines *per se*, including, *inter alia*, press releases etc should be examined to ensure that it did not contravene the Code.

The Panel noted that the press release was entitled 'Novartis drug Galvus approved in EU for type 2 diabetes patients with moderate or severe renal impairment with limited treatment options'. Underneath the title were two bullet points; the first referred to the percentage of patients with type 2 diabetes affected by renal impairment (25%) and the second stated 'Majority of currently available medications are not recommended, contraindicated or have to be taken with caution in this population'. The press release went on to state that the approval of Galvus for use in this patient population 'expands treatment options for patient with moderate or severe renal impairment'. It also quoted a Novartis employee from the global company stating that the approval provided physicians with a '…much-needed new treatment to control blood sugar in a vulnerable patient population…'.

The Panel noted Novartis's submission that of 19 medicines available to treat type 2 diabetes (not including insulin), only three were indicated without the need for caution in both moderate or severe renal impairment. Two products were mentioned by the complainant. Onglyza could only be used at a lower dose and in severe renal impairment with an additional advisory caution. Trajenta could be used without caution or dose adjustment in severe renal failure. The Galvus summary of product characteristics (SPC) gave a recommended daily dose of 100mg when used in dual combination (which metformin or a thiazolidinedione) and 50mg once daily when used in dual combination with a sulphonylurea. There was a dose adjustment in moderate or severe renal impairment or with end stage renal disease when the recommended dose was 50mg once daily.

The Panel noted the statement quoted by the complainant from the press release 'Controlling blood sugar levels in patients with type 2 diabetes and renal impairment can be complex as many oral anti-diabetic medicines are not recommended for use, are contraindicated or should be used with caution'. Given that the title of the press release referred to '…limited treatment options', the text referred to 'few treatment options' and 'expanding treatment options', the Panel did not consider that

the press release conveyed that Galvus had 'plugged a gap in the market' as alleged. It was clear from the press release that there were already 'a few' treatment options available and that Galvus had added to these. No breach of Clause 7.2 was ruled.

The Panel noted the complainant's comment that the Cavanaugh article was out-of-date. This reference was cited in support of the claim that there were few treatment options available in type 2 diabetics with renal impairment. The Panel noted that since this paper had been published, at least two medicines (Onglyza and Trajenta) and Galvus had been approved for use in this patient population. It might be argued that this was not the impression given by the use of a 2007 reference. On balance, however, the Panel considered that it was still the case that treatment options were limited. No breach of Clause 7.2 was ruled.

The Panel noted its rulings of no breach of Clause 7.2 and thus considered that in this regard the content of press release had not failed to meet the requirements of Clause 22.2. Thus no breach of that clause was ruled.

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

Complaint received **7 December 2011**

Case completed **3 February 2012**

CASE AUTH/2465/12/11

PCT PRESCRIBING SUPPORT PHARMACIST v ASTELLAS

Qutenza journal insert

A prescribing support pharmacist at a primary care trust (PCT) complained about a loose insert for Qutenza (capsaicin patch) issued by Astellas which was placed in Guidelines in Practice, November 2011.

The advertisement was headed 'Consensus statement on the use of Qutenza … in peripheral neuropathic pain'. Beneath the heading 'Recommendations of the Consensus Panel' was a diagram headed 'Qutenza may be considered for the treatment of peripheral neuropathic pain at any stage in the algorithm alone or in combination with other therapies'. There then followed an algorithm including first, second and third line treatments for neuropathic pain (excluding diabetic patients). To the right of the algorithm was an indication that Qutenza could be considered at any point in this algorithm (ie first, second or third line). Beneath the algorithm was the statement 'A suggested Drug Treatment Algorithm adapted from NICE [National Institute for Health and Clinical Excellence] Guidelines. Please refer to full NICE Guidelines for further details'.

Whilst the advertisement stated in tiny print that the meeting and resulting consensus statement document were entirely funded and organised by Astellas, the complainant strongly objected to the use of a NICE guidance treatment algorithm for pain, with Qutenza, (never assessed by NICE) sitting within its guidance. A tag at the bottom stated 'A suggested Drug Treatment Algorithm adapted from NICE Guidelines'.

The complainant alleged that this was misleading, particularly as the style and presentation mimicked NICE guidelines. The complainant suggested that if NICE was to assess Qutenza it would almost certainly not be positioned as shown in the advertisement as potentially a first line treatment.

The detailed response from Astellas is given below.

The Panel noted that the prominent title of the advertisement was 'Consensus statement on the use of QUTENZA (capsaicin 8% w/w) in peripheral neuropathic pain'. The fact that the consensus statement resulted from a meeting of eight health professionals that was organised and entirely funded by Astellas was not clear at the outset. A statement explaining the position appeared as paragraph four of the document, approximately half way down the first page in a small font size. The Panel considered that the initial impression created by the title was that the 'consensus' was reached by an independent authority, rather than an Astellas advisory board. The Panel considered that the title was misleading in this regard and ruled a breach of the Code.

The Panel examined the algorithm for the treatment of peripheral neuropathic pain which depicted first, second and third line therapy for neuropathic pain (excluding diabetic patients). To the right of the algorithm a diagram indicated that Qutenza could be considered at any point (ie first, second or third line). Beneath the algorithm and the Qutenza diagram was the statement 'A suggested Drug Treatment Algorithm adapted from NICE Guidelines. Please refer to full NICE Guidelines for further detail'.

The Panel considered that the advertisement was not sufficiently clear that the medicine had not been reviewed by NICE. Some readers would indeed gain the misleading impression that Qutenza had been reviewed by NICE. This was compounded by the content and layout of the page which implied that there was detail about Qutenza in the full NICE Guidelines and by the fact that the algorithm was presented in a similar, albeit simplified, flowchart to that used in the NICE clinical guideline. The Panel considered the advertisement was misleading about the status of Qutenza in relation to NICE and the content of the NICE guideline as alleged. A breach of the Code was ruled.

A prescribing support pharmacist, at a primary care trust (PCT), complained about a loose insert (ref QUT11153UK) for Qutenza (capsaicin patch) issued by Astellas Pharma Ltd which was placed in Guidelines in Practice, November 2011. An electronic version was also available to subscribers of Guidelines in Practice.

The advertisement was headed 'Consensus statement on the use of Qutenza … in peripheral neuropathic pain'. Beneath the heading 'Recommendations of the Consensus Panel' was a diagram headed 'Qutenza may be considered for the treatment of peripheral neuropathic pain at any stage in the algorithm alone or in combination with other therapies'. There then followed an algorithm including first line, second line and third line treatments for neuropathic pain (excluding diabetic patients). To the right of the algorithm was an indication that Qutenza could be considered at any point in this algorithm (ie first, second or third line). Beneath the algorithm was the statement 'A suggested Drug Treatment Algorithm adapted from NICE [National Institute for Health and Clinical Excellence] Guidelines. Please refer to full NICE Guidelines for further details'.

COMPLAINT

The complainant noted that although the advertisement stated in tiny print that the meeting and resulting consensus statement document were entirely funded and organised by Astellas Pharma

Ltd, she strongly objected to the use of a NICE guidance drug treatment algorithm for pain, with Qutenza, (never assessed by NICE) sitting within its guidance. A tag at the bottom stated 'A suggested Drug Treatment Algorithm adapted from NICE Guidelines'.

The complainant alleged that this was misleading, particularly as the style and presentation mimicked NICE guidelines. The complainant also suggested that if NICE did assess Qutenza it would almost certainly not be positioned as shown in the advertisement as potentially a first line treatment.

The complainant queried whether Astellas had the right (under copyright) to publish this altered version.

When writing to Astellas, the Authority asked it to consider Clause 7.2 of the Code.

RESPONSE

Astellas stated that the Qutenza consensus advisory board was implemented in order to provide guidance, based on expert opinion, on the use of Qutenza in a real-life clinical context in the UK. The advertisement at issue was an outcome of this meeting.

The item was clearly presented as promotional material; it contained prescribing information, the Astellas company logo, text stated that 'Both the meeting and resulting consensus statement were entirely funded and organised by Astellas Pharma Ltd', a heading declared that the insert was a 'Promotional Article' and it was in a significantly different style to the Guidelines in Practice publication.

The NICE guidance 'The pharmacological management of neuropathic pain in adults in non-specialist settings' was the only UK specific guidance available for the treatment of neuropathic pain and as such provided the logical basis for discussion as to where Qutenza would fit into a treatment algorithm for peripheral neuropathic pain.

The diagram of the treatment algorithm proposed by the advisory board was labelled with the text 'A suggested Drug Treatment Algorithm adapted from NICE Guidelines'. This wording informed the reader that this was a proposed, original care pathway based on the NICE guideline but with no suggestion that Qutenza had been assessed by NICE which, as the complainant rightly stated, it had not. The reader was also referred to the original guideline. Additionally, the diagram itself was within the section of the statement titled 'Recommendations of the Consensus Panel' and as such was defined as an outcome of the advisory board meeting rather than a reproduction of an existing guideline.

Astellas submitted that although the presentation of this algorithm as a flow chart was similar to the NICE guideline, the content had been substantially altered and the associated text as described above clearly indicated that this was not a reproduction of the guideline itself.

As there was no claim that Qutenza had been assessed by NICE, there was no agreement in place between Astellas and NICE regarding this material.

In summary, Astellas considered that the clear declaration of Astellas' involvement in producing this piece, the stated promotional nature of the piece and the clear explanation of the origins of the consensus advisory board members meant that it had been completely transparent and had not attempted to suggest that NICE had reviewed Qutenza. Astellas therefore did not consider that this piece breached Clause 7.2 as alleged.

PANEL RULING

The Panel noted that at the top right hand corner of the first page of the document was the statement 'Promotional Article'. In addition, the document included prescribing information on the reverse, the Qutenza logo appeared clearly on the bottom right hand corner of the first page and the Astellas company logo appeared opposite this. The Panel considered that it was clear that this was a promotional piece placed by the company.

The Panel noted that the prominent title of the advertisement was 'Consensus statement on the use of QUTENZA (capsaicin 8% w/w) in peripheral neuropathic pain'. The fact that the consensus statement resulted from a meeting of eight health professionals that was organised and entirely funded by Astellas was not clear at the outset. A statement 'Both the meeting and resulting consensus statement document were entirely funded and organised by Astellas ...' only appeared as paragraph four of the document, approximately half way down the first page in a small font size. The Panel considered that the initial impression created by the title was that the 'consensus' was reached by an independent authority, rather than an Astellas advisory board. The Panel considered that the title was misleading in this regard and ruled a breach of Clause 7.2.

The Panel examined the algorithm for the treatment of peripheral neuropathic pain which depicted first, second and third line therapy for neuropathic pain (excluding diabetic patients). First and second line treatments were either amitriptyline or pregabalin or a combination of the two. Third line treatments were 'refer and consider Tramadol or Lidocaine 5% plaster'. To the right of the algorithm a diagram indicated that Qutenza could be considered at any point in the algorithm (ie first, second or third line). Beneath the algorithm and the Qutenza diagram was the statement 'A suggested Drug Treatment Algorithm adapted from NICE Guidelines. Please refer to full NICE Guidelines for further detail'.

The Panel considered that the advertisement was not sufficiently clear that the medicine had not been reviewed by NICE. Some readers would indeed gain the misleading impression that Qutenza had been

reviewed by NICE. This was compounded by the content and layout of the page which implied that there was detail about Qutenza in the full NICE Guidelines and by the fact that the algorithm was presented in a similar, albeit simplified, flowchart to that used in the NICE clinical guideline. The Panel considered the advertisement was misleading about the status of Qutenza in relation to NICE and the content of the NICE guideline as alleged. A breach of Clause 7.2 was ruled.

Complaint received	**13 September 2011**
Case completed	**27 January 2012**

CASES AUTH/2467/12/11 and AUTH/2468/12/11

ANONYMOUS v BOEHRINGER INGELHEIM and PFIZER

Promotion of Spiriva

An anonymous respiratory physician complained about conference material for a meeting of the British Thoracic Society and about materials made available from the joint Boehringer Ingelheim and Pfizer stand at that meeting. The two companies co-promoted Spiriva (tiotropium inhalation powder) and Spiriva Respimat (tiotropium solution for inhalation). Spiriva powder was administered via a Handihaler and Spiriva Respimat via a Respimat inhaler. Spiriva was indicated as maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease.

The detailed response from Boehringer Ingelheim and Pfizer is given below.

The complainant was concerned that the brief description of the Boehringer Ingelheim and Pfizer stand, contained in the conference booklet, stated that Spiriva and the Respimat inhaler were 'new' when in fact both were several years old.

The Panel noted that the Code required that 'new' must not be used to describe, *inter alia*, any product or presentation which had been generally available for more than twelve months in the UK. Both Spiriva and Spiriva Respimat had been generally available for more than 12 months when the meeting in question was held. The Panel ruled a breach of the Code as acknowledged by the companies.

The complainant stated that Boehringer Ingelheim representatives had handed out samples and devices of both the HandiHaler and Respimat at the promotional stand and this was not allowed.

The Panel noted the companies' submission that the items at issue were placebo demonstration devices. The Panel thus considered that they were not samples as defined by the Code and no breach of the Code was ruled in that regard.

The Panel noted that the Code stated, inter alia, that health professionals might be provided with items which were to be passed on to patients and which were part of a formal patient support programme. Such items must be inexpensive and directly benefit patient care; they must not be given out from exhibition stands. Supplementary information to the Code noted that in limited circumstances, such items might be made available for use by health professionals even though they were not to be passed on to patients for them to keep, eg inhalation devices. The Panel considered, however, that the supplementary information did not over-ride the requirement that patient support items could not be given out to health professionals from exhibition stands. The Panel disagreed with the companies' submission that this requirement did not apply to items that were not to be passed to patients. With regard to the provision of the demonstration Handihalers and Respimat inhalers from an exhibition stand the Panel thus ruled a breach of the Code.

An anonymous respiratory physician, complained about conference material for the Winter 2011 meeting of the British Thoracic Society (BTS) and about materials made available from the joint Boehringer Ingelheim Limited and Pfizer Limited stand at that conference. The two companies co-promoted Spiriva (tiotropium inhalation powder) and Spiriva Respimat (tiotropium solution for inhalation). Spiriva powder was administered via a Handihaler and the Spiriva Respimat via a Respimat inhaler. Spiriva was indicated as maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

Boehringer Ingelheim responded on behalf of both companies.

A Conference programme and abstracts booklet

A page of the conference programme and abstracts booklet headed 'Exhibitors' Information', included a brief description of Boehringer Ingelheim's and Pfizer's joint stand which included a statement that Boehringer Ingelheim was '... committed to delivering high-quality respiratory care through the discovery of new respiratory medicines (Spiriva) and delivery systems (Respimat) ...'. This was followed by a short paragraph about Pfizer Inc.

COMPLAINT

The complainant was concerned that the exhibitors' information used the word 'new' when the medicines mentioned were several years old and there was nothing new about them.

When writing to Boehringer Ingelheim and Pfizer, the Authority asked each to respond in relation to Clause 7.11 of the Code.

RESPONSE

Boehringer Ingelheim accepted that the word 'new' in relation to Spiriva HandiHaler and Spiriva Respimat was used inappropriately; the oversight was regretted and the statement had been withdrawn. It would be amended if used again. In order to ensure this did not happen again, training would be provided to relevant personnel. Processes would be implemented to ensure future exhibitor information was certified appropriately.

Boehringer Ingelheim submitted that Spiriva was first authorized in May 2002 and Spiriva Respimat in September 2007.

PANEL RULING

The Panel noted that Clause 7.11 required that the word 'new' must not be used to describe any product or presentation which had been generally

available, or any therapeutic indication which had been generally promoted, for more than twelve months in the UK. The Panel noted Boehringer Ingelheim's submission that marketing authorizations had been granted for Spiriva in 2002 and for Spiriva Respimat in 2007. Both products had therefore been generally available for more than 12 months when the BTS Winter meeting 2011 was held. The Panel noted that Boehringer Ingelheim had acknowledged that the use of the word 'new' was inappropriate. A breach of Clause 7.11 was ruled.

B Provision of demonstration inhaler devices from an exhibition stand

COMPLAINT

The complainant alleged that Boehringer Ingelheim representatives had handed out samples and devices of both the HandiHaler and Respimat at the promotional stand. The complainant was sure that this was not allowed.

When writing to Boehringer Ingelheim and Pfizer, the Authority asked each to respond in relation to Clauses 17.3 and 18.2 of the Code.

RESPONSE

Boehringer Ingelheim submitted that active samples were not distributed from the promotional stand therefore Clause 17.3 did not apply. Boehringer Ingelheim company policy was not to distribute active samples on request. Placebo HandiHaler and placebo Respimat devices were demonstrated and made available to health professionals by representatives upon request as permitted under Clause 18.2. The representatives at the stand had twenty such devices available to them.

Boehringer Ingelheim noted that the supplementary information for Clause 18.2 stated that:

> 'Although items which are to be passed on to patients may not be given out from exhibition stands, they may be exhibited and demonstrated on stands and requests for them accepted for later delivery.' (emphasis added)

Boehringer Ingelheim considered that since these were not items to be passed to patients the above requirement of Clause 18.2 that giving out such items at exhibition stands should not take place did not apply.

Boehringer Ingelheim noted that the supplementary information to Clause 18.2 further stipulated, particularly citing the example of inhalation devices, that such items might be made available to health professionals in promotional calls or other circumstances:

> 'Patient support items may be provided to health professionals by representatives during the course of a promotional call and representatives may deliver such items when they are requested by health professionals, for example on reply paid cards. Provided that they have been appropriately documented and certified in advance as required by Clause 14.3, in limited circumstances patient support items may be made available for the use of health professionals even though they are not to be passed on to patients for them to keep. This is where their purpose is to allow patients to gain experience in using their medicines whilst under the supervision of a health professional. Examples include inhalation devices (with no active ingredient) and devices intended to assist patients to learn how to self-inject.' (emphasis added)

Boehringer Ingelheim submitted that it had complied with the requirements of Clause 18.2 in making placebo inhalation devices available to health professionals.

PANEL RULING

The Panel noted that Clause 17.3 required that samples were only supplied in response to written requests which had been signed and dated. The supplementary information to Clause 17 defined a sample as a small supply of a medicine provided to health professionals so that they might familiarise themselves with it and acquire experience in dealing with it. The supply of a product which was not a medicine because it did not contain the active ingredient was not regarded as the supply of a sample.

The Panel noted Boehringer Ingelheim's submission that the items at issue on the exhibition stand were placebo demonstration devices. The Panel thus considered that they were not samples as defined by the Code and so Clause 17.3 did not apply. No breach of Clause 17.3 was ruled.

The Panel noted that Clause 18.2 stated, *inter alia*, that health professionals might be provided with items which were to be passed on to patients and which were part of a formal patient support programme. The items provided must be inexpensive and directly benefit patient care. They might bear the name of the company providing them. They must not be given out from exhibition stands. The supplementary information to Clause 18.2, Patient Support Items, noted that in limited circumstances, such items might be made available for use by health professionals even though they were not to be passed on to patients for them to keep. Inhalation devices were cited as an example of such items. The Panel considered, however, that the supplementary information did not over-ride the requirement of Clause 18.2 that patient support items could not be given out to health professionals from exhibitions stands. The Panel disagreed with Boehringer Ingelheim's submission that this requirement did not apply to items that were not intended to be passed to patients.

The Panel considered that the provision of the demonstration Handihalers and Respimat inhalers from an exhibition stand was contrary to Clause 18.2 and a breach of that clause was ruled.

Complaint received **19 December 2011**

Case completed **7 February 2012**

CASE AUTH/2469/12/11

VOLUNTARY ADMISSION BY BAYER

Symposium invitation

Bayer advised the Authority that, in its view, an invitation to a company sponsored symposium was in breach of the Code. The invitation, which promoted Levitra (vardenafil), had been prepared and distributed by Bayer global. Bayer global had not regarded the invitation as promotional and had thus not followed the relevant standard operating procedure (SOP). As a consequence the invitation had not been certified for UK use. Some of the invitations had been sent to UK recipients.

Bayer submitted that the invitation did not include the prescribing information and other obligatory information as required by the Code. Further, a strapline 'First-line ED [erectile dysfunction] therapy he can take any time, anywhere' was included although this was not approved for use in the UK.

In addition Bayer noted that the invitation had been sent in transparent envelopes thus the public could see the brand name and the fact that the product was related to sexual medicine. Finally, the invitation had been sent to some people whom Bayer understood were not health professionals.

In accordance with the Constitution and Procedure, this matter was taken up as a complaint under the Code.

The detailed response from Bayer is set out below.

The Panel noted that the invitation to a symposium in Italy had been created and distributed by the Bayer global team. The Code required that activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities took place or the materials were used. The invitation in question was issued from a company based in Germany but insomuch as it was sent to UK recipients, the Panel considered that that aspect of its use came within the scope of the Code. As the invitation was promotional and had not been certified for use in the UK, the Panel ruled a breach of the Code.

As the non-proprietary name was not included next to the most prominent display of the brand name, there was no prescribing information and no statement regarding adverse event reporting, breaches of the Code were ruled.

With regard to the strapline, 'First-line ED therapy he can take anytime, anywhere', the Panel noted that the maximum dose of Levitra was one tablet daily. The Panel thus considered that, depending on when the last dose was taken, Levitra could not be taken 'anytime'. The Panel thus considered that the strapline was inconsistent with the particulars listed in the Levitra summary of product characteristics (SPC). A breach of the Code was ruled.

The Panel noted that the invitation was sent in a transparent envelope such that the public could see the Levitra product logo on the front cover of the invitation and enough additional information to assume that Levitra was a medicine used in sexual health. In that regard the Panel considered that Levitra had been advertised to the public. Breaches of the Code were ruled.

The Panel noted that some of the recipients of the invitation were employees of another pharmaceutical company and others were employed by an agency representing a pharmaceutical company. Bayer had submitted that none of these recipients were health professionals. The Panel noted that they could also not be considered to be appropriate administrative staff. The Panel considered that the invitation, which promoted Levitra, had thus been sent to a small number of members of the public. A breach of the Code was ruled.

The Panel noted that Bayer had acknowledged all of the above breaches of the Code.

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

The Panel noted that Bayer's global SOP relating to the review and approval of promotional material clearly referred to the need for material to be consistent with, *inter alia*, local codes and to the need for country material to be reviewed and approved by country medical affairs. There was thus a global SOP which should have prevented the invitation being used in the UK without being appropriately certified. The Panel considered that Bayer had been badly let down by global colleagues who failed to regard the invitation as promotional material and consequently failed to follow company procedures. Nonetheless the Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of that clause was ruled.

Bayer Healthcare in the UK voluntarily advised the Authority that, in its view, an invitation to a Bayer sponsored satellite symposium organised by Bayer global headquarters, Berlin, was in breach of the Code.

The symposium, held at the European Society for Sexual Medicine (ESSM) Congress in Milan in December 2011, was entitled 'Men's changing sexuality, identity and behaviour'; it was conducted by a faculty of four non-UK clinicians. The invitations were sent by Bayer global to delegates registered for the ESSM. Seventy four invitations were sent to UK delegates.

The four page, A5 invitation featured the Levitra (vardenafil) orodispersible tablets (ODT) logo prominently on the front cover. The front cover stated the title of the symposium and gave details of the time and place. Page two gave brief details of the four speakers and page three outlined the meeting programme. The Levitra product logo appeared in the bottom right hand corner together with the strapline 'First-line ED [erectile dysfunction] therapy he can take anytime, anywhere'. The centre of the back page featured a roundel showing a photograph of Milan and the Bayer Healthcare logo appeared in the bottom left hand corner.

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

COMPLAINT

In late November 2011, Bayer global informed Bayer Healthcare that the invitation to the symposium had been posted earlier that month without obtaining UK approval of the invitation as required by the Code.

The invitation was prepared by global strategic marketing and approved by global medical affairs at Bayer global headquarters in Berlin. The invitation and the content of the symposium promoted Levitra. However, Bayer Healthcare submitted that the invitation did not include prescribing information as it was mistakenly not regarded as promotional by those who prepared and approved it through the global approval system. Consequently Bayer Healthcare believed that this was in breach of Clause 4.1. The invitation did not include an adverse event reporting statement, in breach of Clause 4.10.

Bayer Healthcare submitted that the invitation also failed to include the non-proprietary name (vardenafil) adjacent to the most prominent display of the Levitra brand name on the front cover of the invitation in breach of Clause 4.3. The non-proprietary name was included next to the later inclusion of the brand name on the inside cover.

The inside cover of the invitation included the strapline 'First-line ED therapy he can take anytime, anywhere' beneath the Levitra logo. Bayer Healthcare noted that this claim was not approved for use in the UK as Levitra should only be taken as a maximum of 1 tablet per 24 hours and was a breach of Clause 3.2.

The review and approval processes for marketing and educational materials were defined by a Bayer global standard operating procedure (SOP) which Bayer Healthcare considered clearly stated the company's commitment to comply with the IFPMA and EFPIA Codes. This SOP required all materials to be reviewed and approved at a global, regional and local country level. However, in this instance, there was a failure to obtain UK review and approval of the invitation and mailing. As such the invitation and mailing for UK health professionals was not certified, in breach of Clause 14.1.

Bayer Healthcare noted that the invitation was sent in a transparent envelope to health professionals in several countries, including the UK. This meant that the public could see the brand name and, although the indication was not visible, that the product was related in some way to sexual medicine. This was a breach of Clause 9.8. The use of the transparent envelope arose through a lack of supervision of the third party contractor engaged by the Levitra global product manager and failure of the envelope to be submitted for approval into the global approval system.

The invitation was also sent directly to people in another pharmaceutical company and to others in an events agency. Bayer Healthcare understood that none of these individuals were health professionals. Consequently Bayer Healthcare considered this was a breach of Clause 22.1.

Bayer Healthcare submitted that it took this breach of internal procedure and failure to comply with the Code extremely seriously and was working with global colleagues in Berlin to ensure that similar circumstances did not arise again. In late December senior officers from Bayer global's compliance, medical affairs and legal departments met senior Bayer Healthcare medical, legal and compliance colleagues to discuss how to prevent such circumstances arising again. On the previous day, the men's health global marketing team in Berlin had been re-trained on compliance.

When writing to Bayer Healthcare the Authority asked it to provide any further comments in relation to Clauses 2, and 9.1 of the Code.

RESPONSE

In relation to the requirements of Clauses 2 and 9.1, Bayer Healthcare stated that the SOP set out a clearly defined procedure for the review and approval of marketing and educational materials. It clearly stated Bayer's commitment to comply with the IFPMA and EFPIA Codes and required global promotional materials, in addition to global review and approval, to be reviewed at a country level if such material was to be distributed to external persons in that country.

Bayer Healthcare submitted that the company therefore had a clear procedure and instructions in place to ensure that global material intended for UK distribution was reviewed in the UK for compliance with the Code. The incident at issue arose because two individuals from Bayer's headquarters failed to follow the SOP. The individuals concerned were last trained on the SOP in 2009.

Bayer Healthcare submitted that if the materials had been submitted for approval in the UK in accordance with the SOP, they would not have been approved, as the medical department in the UK, which subsequently became aware of the existence of the UK invitations, was itself responsible for the internal reporting and voluntary admission of the incident.

Consequently, Bayer Healthcare acknowledged that it

had failed to maintain high standards in breach of Clause 9.1.

With regard to Clause 2, Bayer Healthcare emphasised that immediately after internally being made aware of the incident, it began a thorough internal investigation. As soon as this detailed investigation was finished, and Bayer Healthcare was confident that all relevant information had been collated, a voluntary admission was sent to the PMCPA.

Bayer Healthcare submitted that it had initiated prompt corrective action by implementing compliance retraining of the global marketing team concerned in December 2011 and was organising compliance retraining of the men's health global medical team. In addition, the breaches outlined were discussed at a legal and compliance meeting with senior global colleagues in December 2011. As a consequence, the importance of local country approvals had been re-emphasised.

PANEL RULING

The Panel noted that the invitation to a symposium in Italy had been created and distributed by the Bayer global team. The supplementary information to Clause 1.8, Applicability of Codes, required that activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities took place or the materials were used. The invitation in question was issued from a company based in Germany but insomuch as it was sent to UK recipients, the Panel considered that that aspect of its use came within the scope of the Code. As the invitation was promotional and had not been certified for use in the UK, the Panel ruled a breach of Clause 14.1.

The Panel noted that the Levitra product logo featured prominently on the front cover of the invitation and was also included on page three. The Panel considered that, as submitted by Bayer Healthcare, the invitation promoted Levitra and it therefore needed to incorporate prescribing and other obligatory information as required by Clause 4 of the Code. The Panel noted that as the front cover of the invitation featured the most prominent display of the brand name, the non-proprietary name should have appeared immediately adjacent to it. As the non-proprietary name was not included next to the brand logo on the front cover the Panel ruled a breach of Clause 4.3. The Panel further noted that the invitation should have included the Levitra prescribing information and as it did not a breach of Clause 4.1 was ruled. The invitation also did not include a statement regarding adverse event reporting. A breach of Clause 4.10 was ruled.

With regard to the strapline which appeared under the product logo on page three of the invitation, 'First-line ED therapy he can take anytime, anywhere', the Panel noted that the maximum dose of Levitra ODT was one tablet daily. The Panel thus considered that, depending on when the last dose was taken, Levitra ODT could not be taken 'anytime'. The Panel thus considered that the strapline was inconsistent with the particulars listed in the Levitra summary of product characteristics (SPC). A breach of Clause 3.2 was ruled.

The Panel noted that the invitation was sent in a transparent envelope onto which was stuck an address label and a stamp. The transparency of the envelope meant that the public could see the Levitra product logo on the front cover of the invitation and an incomplete reference to the ESSM (from the example provided the public would only see 'European Society for Sexual Medic', the rest of the text was obscured by the address label). Clause 9.8 of the Code required that exposed mailings, envelopes or wrappers must not carry matter which might be regarded as advertising to the public, contrary to Clause 22.1. The Panel noted that from the information which could be seen through the envelope, members of the public would assume that Levitra was a medicine used in sexual health. In that regard the Panel considered that Levitra had been advertised to the public. Breaches of Clauses 9.8 and 22.1 were ruled.

The Panel noted that some of the recipients of the invitation were employees of another pharmaceutical company and others were employed by an agency representing a pharmaceutical company. Bayer Healthcare had submitted that none of these recipients were health professionals. The Panel noted that they could also not be considered to be appropriate administrative staff. The Panel considered that the invitation, which promoted Levitra, had thus been sent to a small number of members of the public. A breach of Clause 22.1 was ruled.

The Panel noted that Bayer Healthcare had acknowledged all of the above breaches of the Code.

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

The Panel noted that Bayer's global SOP relating to the review and approval of promotional material clearly referred to the need for material to be consistent with, *inter alia*, local codes. It stated that country promotional material must only be used upon review and approval by country medical affairs. The Panel noted that Bayer global thus had an SOP in place which should have prevented the invitation being used in the UK without being appropriately certified. The Panel considered that Bayer Healthcare had been badly let down by global colleagues who failed to regard the invitation as promotional material and consequently failed to follow the procedures laid out in the relevant SOP. Nonetheless the Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

Complaint received **22 December 2011**

Case completed **13 February 2012**

CASE AUTH/2470/1/12

ANONYMOUS v NOVO NORDISK

Arrangements for a meeting

An anonymous, non-contactable, health professional alleged that in mid December 2011 Novo Nordisk and Sanofi (see Case AUTH/2471/1/12) had paid for what was clearly a Christmas party for the clinicians, nurses and administrative staff of the local diabetes team.

The evening meeting, which was at a local restaurant, was organised between the clinical lead consultant and the representatives involved.

The complainant stated that the supposed agenda did not materialise, that there was a partition to supposedly separate representative stands and that a representative from another company arrived but then left.

The detailed response from Novo Nordisk is given below.

The Panel noted that Novo Nordisk described the event as an evening hospital departmental meeting to launch the inpatient diabetes service and discuss plans for the future of the local diabetes service.

The Panel noted Novo Nordisk's submission that the representative agreed to sponsor the meeting organised by the clinical lead for diabetes subject to the venue being appropriate and seeing the agenda. The representative had not influenced the agenda or selection of speakers. Nonetheless the Panel considered that companies sponsoring meetings organised by a third party had to satisfy themselves that all of the arrangements, including the venue and invitation, complied with the Code.

The Panel was very concerned that three emails between the representative and meeting organiser, dated 15 and 16 November, were the sole written correspondence about the event. The first email was an invitation from the meeting organiser to departmental staff and bore the subject title 'FW: Christmas at [named restaurant] 15th of December'. The first paragraph referred to previous correspondence and positive responses and confirmed the date of the 'Xmas meal' at the restaurant. The event was described as an opportunity to catch up and 'develop trust, hope and most importantly happiness across our units'. There was a brief outline of the proposed agenda and then the penultimate paragraph read 'The meal: 07.30 [sic] – late'. The invitation appeared to have then been forwarded in a second email, sent six minutes later and also with the subject title 'FW: Christmas at [named restaurant] 15th of December', from the meeting organiser to the representative which listed four meeting topics and asked the representative if she would like five minutes. It was unclear whether the representative saw the final agenda which differed from that described in the email prior to the event. In the third email the representative stated that the agenda looked good and reminded the organiser that there needed to be a private meeting room and 1½ hours of presentation and discussion to comply with the Code. The representative explained that she could pay for wine, beer and soft drinks in moderation but that spirits would have to be paid for individually.

The Panel noted that whilst it had not seen all of the correspondence between the meeting organiser and his colleagues it considered that the email invitation dated 15 November implied that the meeting was primarily a social event. It was described as a Xmas meal which finished late in the evening. This would certainly be the impression given to invitees. This was compounded by the fact that it was an evening event in a restaurant ten days before Christmas. In the Panel's view it was difficult to understand why the company decided that it was an appropriate meeting to sponsor given the unacceptable wording of the invitation.

The Panel noted that, according to the agenda, the meeting began at 7pm, featured two short presentations and finished with a question and answer session at 7.50pm. The six slides presented by one of the consultants detailed his background, clinical interests and reasons for moving to the area. The Panel queried the educational content of the presentation and whether this was a suitable presentation for the industry to sponsor. According to Novo Nordisk, due to a late start at 7.20pm, the session finished at 8.40pm and discussions continued over dinner.

The Panel noted that the restaurant did not charge room hire. The representative had visited the restaurant prior to the event to satisfy herself that the arrangements were acceptable. The Panel noted that whilst Novo Nordisk's description of the layout and floor plan sketch indicated a degree of separation between the public part of the restaurant and the meeting, the arrangements were not such as to constitute a private room and the Panel queried whether in that regard the arrangements were acceptable and noted that according to Novo Nordisk, a representative from a third company had departed shortly after arrival due to concerns that the meeting room did not have a door. A similar comment was made by the complainant.

The total cost per head for the evening, to include drinks, was £32.81. Novo Nordisk paid £450 and the credit card receipt showed that the bill was paid at 10.42pm.

Overall the Panel was very concerned about the impression given by the arrangements. Although

the email invitation to the meeting had been sent by the meeting organiser, it was extremely important that representatives controlled the arrangements for meetings which they sponsored. Although the representative had referred to the need for 90 minutes of presentation and discussion there had been no more than 1 hour of education. The invitation and the overall arrangements implied that the evening was primarily a Christmas social event and it would have been on this basis that the delegates had agreed to attend. A breach of the Code was ruled which was appealed by Novo Nordisk. The Panel considered that both the representative and company had failed to maintain high standards. A breach of the Code was ruled which was not appealed.

The Panel noted that a primarily social event at Christmas had been sponsored by, *inter alia*, Novo Nordisk. Although the meeting was initiated and organised by a local clinician, it was beholden upon the company to check that all of the arrangements were consistent with the Code and in the view of the Panel the company had not met its obligations in this regard. The email invitation and subsequent email to the representative should have triggered a review of the arrangements. None of the meeting materials before the Panel contained a declaration of the company's sponsorship as required by the Code. The Panel considered that overall the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed by Novo Nordisk.

The Appeal Board noted that the representative had agreed to sponsor the meeting after the organiser had already emailed potential attendees describing the event as 'Christmas at [named restaurant] 'and the 'Xmas meal'. The impression given by the email was that the educational part of the event had been added on to the main purpose which was the departmental Christmas meal. The representative was sent a copy of that email. Although her reply, dated 16 November, reminded the organiser about the need for a private room and 1½ hours of education she did not try to correct the impression that the main reason for the meeting was the departmental Christmas meal. The meeting was held on 15 December and in the Appeal Board's view the representative had time and should have done more to ensure that the arrangements for the meeting, and the impression of those arrangements, complied with the Code. There was no written agreement between the representative and the meeting organiser, only a brief exchange of emails. The representative had checked the venue.

The Appeal Board noted from the company's representatives at the appeal that as the representative at issue was experienced, it was her responsibility to ensure that all of the arrangements for the meeting complied with the Code. To that end representatives were trained on the Code and the company's standard operating procedure (SOP) on meetings and hospitality. The Appeal Board was concerned that although Novo Nordisk had accepted the ruling of a breach of the Code the company's representatives at the appeal were confident that its representative knew the requirements of the SOP.

The Appeal Board considered that Novo Nordisk had taken inadequate measures to ensure that the arrangements for the pre-organised meeting which its representative had agreed to sponsor complied with the Code. The Appeal Board noted that the supplementary information to the Code stated that the impression created by the arrangements for any meeting must be kept in mind. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its concerns above, but in light of the educational content, it decided that on balance, the arrangements were not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled. The appeal on this point was successful.

An anonymous, non-contactable, health professional complained about a meeting sponsored by Novo Nordisk Limited and Sanofi (see Case AUTH/2471/1/12) in December 2011 which had taken place at a local restaurant.

COMPLAINT

The complainant was concerned at the blatant disregard by a pharmaceutical company to ethics when promoting medicines. The complainant alleged that in December 2011 Novo Nordisk and Sanofi had paid for what was clearly a Christmas party for the clinicians, nurses and administrative staff of the local diabetes team. The meeting, which the complainant considered was a party, had been organised amicably between the clinical lead consultant and the representatives involved.

The complainant stated that there was a supposed agenda but this did not materialise, that there was a partition to supposedly separate representative stands and that a representative from another company arrived but then left. Diabetes therapy in the trust consisted predominantly of Novo Nordisk products.

When writing to Novo Nordisk, the Authority asked it to consider the requirements of Clauses 2, 9.1, 15.2 and 19.1 of the 2011 Code as the meeting took place in 2011.

RESPONSE

Novo Nordisk explained that the event in question was an evening hospital departmental meeting held in mid December 2011. The meeting was organised by the clinical lead for diabetes in the local foundation trust.

Novo Nordisk submitted that the clinical lead for diabetes approached it, Sanofi and Boehringer Ingelheim to co-sponsor the meeting. Novo Nordisk stated that its representative, who had passed the ABPI Medical Representatives Examination, agreed to sponsor the meeting subject to the venue being

appropriate as well as seeing the meeting agenda. The sponsorship involved Novo Nordisk part sponsoring the meal which followed the presentations made by two local consultants. Novo Nordisk's representative had no influence over the agenda or the selection of speakers.

A copy of an email dated 15 November between the meeting organiser and Novo Nordisk's representative regarding the meeting arrangements was provided. Novo Nordisk stated that while the organiser referred to 'Christmas at [named restaurant]' in the subject box, it was clear from the correspondence that Novo Nordisk's representative referred to the agenda and reminded the organiser of the need for a private room, agenda timings and the confines of hospitality to be provided.

The organiser selected the venue, and told Novo Nordisk's representative that the meeting would be held in a private room. On the evening of the meeting, a Boehringer Ingelheim representative arrived, but left shortly afterwards concerned that the meeting room did not have a door. Novo Nordisk's representative had initially been similarly concerned when she had seen the venue some weeks earlier. While the meeting was non-promotional Novo Nordisk's representative was still keen to ensure that the meeting area was suitably private. The representative's concerns were eradicated when the restaurant manager assured her that no members of the public would be in the restaurant during the meeting and furthermore, any public seating was such a distance away from the meeting room that nothing could be heard or seen.

The meeting was held to launch the inpatient diabetes service and the plans going forward for the trust's diabetes service.

A copy of the meeting agenda was provided. Novo Nordisk submitted that the agenda clearly showed an educational content with two medical consultants speaking. Due to the IT difficulties the meeting started at 7.20pm, later than planned, following the organiser's welcome and introduction. The sessions completed at 8.40pm and discussions continued over dinner.

A list of the delegates was provided including details of those who were invited but did not attend.

The total cost of the food and drinks was £953.15 and was split between Novo Nordisk (£450) and Sanofi (£503.15). The meal choices of each delegate were provided in advance to the restaurant. Thirty delegates provided meal choices but only twenty six attended and so four extra meals were paid for despite no attendance. Taking this into account, the cost per head was £32.80. A copy of the itemised bill was provided.

There were no promotional exhibition stands at the meeting, and no partitions. As a result Novo Nordisk was unclear as to the complainant's statement: 'There was a partition to supposedly separate representative stands'.

Novo Nordisk submitted letters of support from the meeting organiser, clinical lead for diabetes, and one of the consultant speakers regarding the meeting arrangements. Based on the evidence provided, Novo Nordisk concluded that this was a genuine educational meeting with a clear agenda, for which Novo Nordisk sponsored the hospitality. The sponsorship provided was arranged in accordance with Clause 19 of the Code and Novo Nordisk's own meetings and hospitality standard operating procedure. Novo Nordisk denied any breach of Clauses 15.2, 19.1, 9.1 or 2 of the Code.

In response to the case preparation manager's request for further information, Novo Nordisk submitted that the letters from the meeting organiser and one of the speakers had been received after the company had contacted each of them.

In response to the Panel's request for further information Novo Nordisk explained that the meeting was held in a separate part of the restaurant which was accessed through an archway and a small vestibule. The representative was confident that the meeting was totally private and could not be seen or heard from other areas, even though it did not have a door. A sketch of the floor plan of the restaurant was provided.

Novo Nordisk had no further written correspondence between the meeting organiser and its representative other than the email of 15 November. All other communication regarding the meeting arrangements was verbal, either by telephone or during face-to-face meetings.

Novo Nordisk explained that one of the delegates was a GP with a special interest in diabetes. She was invited to the meeting by the clinical lead for diabetes.

Copies of the slides were provided.

PANEL RULING

The Panel noted that Novo Nordisk described the event as an evening hospital departmental meeting to launch the inpatient diabetes service and discuss plans for the future of the local diabetes service.

The Panel noted that the Code permitted companies to provide hospitality within certain parameters as set out in Clause 19.1 which stated that 'The level of subsistence offered must be appropriate and not out of proportion to the occasion. The costs involved must not exceed that level which the recipients would normally adopt when paying for themselves'. The Panel also noted the supplementary information to Clause 19.1, Meetings and Hospitality, which set out certain basic principles for any meeting: the meeting must have a clear educational content, the hospitality associated with the meeting must be secondary to the nature of the meeting and must be appropriate and not out of proportion to the occasion and that any hospitality provided must not extend to spouses and other persons unless that person qualified as a proper delegate or participant

at the meeting in their own right. Administrative staff might be invited to meetings where appropriate. The venue must be appropriate and conducive to the main purpose of the meeting. Further, the Panel noted that the supplementary information also stated that 'The impression that is created by the arrangements for any meeting must always be kept in mind'. In addition, the Panel considered that as a principle, representatives sharing the cost of a meeting would not make otherwise excessive costs acceptable under the Code.

The Panel noted Novo Nordisk's submission that the representative agreed to sponsor the meeting organised by the clinical lead for diabetes subject to the venue being appropriate and seeing the agenda. The representative had not influenced the agenda or selection of speakers. Nonetheless the Panel considered that companies sponsoring meetings organised by a third party had to satisfy themselves that all of the arrangements, including the venue and invitation, complied with the Code.

The Panel was very concerned that three emails between the representative and meeting organiser, dated 15 and 16 November, were the sole written correspondence about the event. The first email was an invitation from the meeting organiser, the clinical lead for diabetes, to departmental staff and bore the subject title 'FW: Christmas at [named restaurant] 15th of December'. The first paragraph referred to previous correspondence and positive responses and confirmed the date of the 'Xmas meal' at the restaurant. The event was described as an opportunity to catch up and 'develop trust, hope and most importantly happiness across our units'. Between 6.30pm and 7.30pm there would be a discussion on diabetes and associated matters for about an hour prior to the meeting delivered by new consultants. The penultimate paragraph read 'The meal: 07.30 [sic] – late'. The invitation appeared to have then been forwarded in a second email, sent six minutes later and also with the subject title 'FW: Christmas at [named restaurant] 15th of December', from the meeting organiser to the representative which listed four meeting topics and asked the representative if she would like five minutes. It was unclear whether the representative saw the final agenda which differed from that described in the email prior to the event. In the third email the representative stated that the agenda looked good and reminded the organiser that there needed to be a private meeting room and 90 minutes of presentation and discussion to comply with the Code. The penultimate paragraph explained that the representative was allowed to pay for wine, beer and soft drinks in moderation but that spirits would have to be paid for individually.

The Panel noted that whilst it had not seen all of the correspondence between the meeting organiser and his colleagues it considered that the email invitation dated 15 November implied that the meeting was primarily a social event. It was described as a Xmas meal which finished late in the evening. This would certainly be the impression given to invitees. This was compounded by the fact that it was an evening event in a restaurant ten days before Christmas. In the Panel's view it was difficult to understand why the company decided that it was an appropriate meeting to sponsor given the unacceptable wording of the invitation.

The Panel noted that, according to the agenda, the meeting began at 7pm and featured two short presentations; 'Diabetes Towards a Sweet Future' (20 minutes) and 'Diabetes in the [local area] – Why Here?' (15 minutes) and finished with a question and answer session at 7.50pm. The six slides presented by one of the consultants detailed his background, clinical interests and reasons for moving to the area. The Panel queried the educational content of the presentation and whether this was a suitable presentation for the industry to sponsor. According to Novo Nordisk, due to a late start at 7.20pm, the session finished at 8.40pm and discussions continued over dinner.

The Panel noted that the meeting took place in a restaurant. No room hire was charged. The representative had visited the restaurant prior to the event to satisfy herself that the arrangements were acceptable. The Panel noted that whilst Novo Nordisk's description of the layout and floor plan sketch indicated a degree of separation between the public part of the restaurant and the meeting, the arrangements were not such as to constitute a private room and the Panel queried whether in that regard the arrangements were acceptable and noted that according to Novo Nordisk, a representative from a third company had departed shortly after arrival due to concerns that the meeting room did not have a door. A similar comment was made by the complainant.

The cost of the meal was £24.95 per head and including drinks the total cost of the evening was £953.15 (including the cost of four meals for non-attendees), of which Novo Nordisk bore £450. The total cost per head for the evening was £32.81. The credit card receipt showed that the bill was paid at 10.42pm.

Overall the Panel was very concerned about the impression given by the arrangements. Although the email invitation to the meeting had been sent by the meeting organiser, it was extremely important that representatives controlled the arrangements for meetings which they sponsored. Although the representative had referred to the need for 90 minutes of presentation and discussion there had been no more than 1 hour of education. The invitation and the overall arrangements implied that the evening was primarily a Christmas social event and it would have been on this basis that the delegates had agreed to attend. A breach of Clause 19.1 was ruled. This ruling was appealed by Novo Nordisk. The Panel considered that both the representative and company had failed to maintain high standards. A breach of Clause 15.2 was ruled. The Panel considered that the alleged breach of Clause 9.1 was covered by its ruling of a breach of Clause 15.2.

The Panel noted that a primarily social event at Christmas had been sponsored by, *inter alia*, Novo Nordisk. Irrespective of the fact that it was initiated and organised by a local clinician, it was beholden upon the company to check that all of the arrangements were consistent with the Code and in the view of the Panel the company had not met its obligations in this regard. The email invitation dated 15 November and the subsequent email to the representative should, at the very least, have triggered a fundamental review of the arrangements. None of the meeting materials before the Panel contained a declaration of the company's sponsorship as required by Clause 19. The Panel considered that overall the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed by Novo Nordisk.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that the meeting which was not arranged to be a social event, was organised to provide the local NHS foundation trust with a clear objective to discuss the inpatient service and future plans for the trust's diabetes service. The two educational presentations together lasted approximately 1 hour 20 minutes and provided the delegates with a better understanding of the diabetes services within the local trust and a greater awareness of the opportunities available to improve the service further.

Novo Nordisk submitted that one speaker gave an insight in to how he intended to integrate into the department and improve the diabetes services currently offered. Whilst the number of slides presented was limited, the speaker provided information on the delivery of foot care in diabetic patients as well as managing diabetes during pregnancy. He also highlighted how he could transfer his skills learnt at another hospital to the trust. Substantial discussion around these two points took place. The other consultant's presentation contained significant content regarding the use of analogue insulins along with a discussion on the cost of treating diabetes and ways to make it more cost effective.

Novo Nordisk noted that both the meeting organiser, the clinical lead for diabetes, and one of the consultant speakers provided supporting letters after the meeting, commenting on how well both presentations had been received.

Novo Nordisk therefore appealed the ruling of a breach of Clause 19.1 as the educational content of the meeting was significant and the hospitality provided was secondary to the purpose of the meeting. Furthermore, the subsistence supplied on the evening was appropriate and not out of proportion to the occasion. Novo Nordisk denied that the arrangements for the meeting brought discredit upon and reduced confidence in the industry, and therefore it also appealed the ruling of a breach of Clause 2.

APPEAL BOARD RULING

The Appeal Board noted that the representative had agreed to sponsor the meeting after the organiser had already emailed potential attendees describing the event as 'Christmas at [named restaurant] 'and the 'Xmas meal'. The impression given by the email was that the educational part of the event had been added on to the main purpose which was the departmental Christmas meal. The representative was sent a copy of that email. Although her reply, dated 16 November, reminded the organiser about the need for a private room and 1½ hours of education she did not try to correct the impression that the main reason for the meeting was the departmental Christmas meal. The meeting was held on 15 December and in the Appeal Board's view the representative had time and should have done more to ensure that the arrangements for the meeting, and the impression of those arrangements, complied with the Code. There was no written agreement between the representative and the meeting organiser, only a brief exchange of emails. The representative had checked the venue.

The Appeal Board noted from the company's representatives at the appeal that as the representative at issue was experienced, the company's burden of ensuring that all the arrangements for the meeting complied with the Code was the representative's responsibility. To that end representatives were trained on the Code and the company's standard operating procedure (SOP) on meetings and hospitality. The Appeal Board was concerned that although Novo Nordisk had accepted the ruling of a breach of Clause 15.2 the company's representatives at the appeal were confident that its representative knew the requirements of the SOP.

The Appeal Board considered that Novo Nordisk had taken inadequate measures to ensure that the arrangements for the pre-organised meeting which its representative had agreed to sponsor complied with the Code. The Appeal Board noted that the supplementary information to Clause 19.1 of the Code stated that the impression created by the arrangements for any meeting must be kept in mind. The Appeal Board upheld the Panel's ruling of a breach of Clause 19.1. The appeal on this point was unsuccessful

The Appeal Board noted its concerns above, but in light of the educational content it decided that on balance the arrangements were not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled. The appeal on this point was successful.

Complaint received	**3 January 2012**
Case completed	**15 May 2012**

CASE AUTH/2471/1/12

ANONYMOUS v SANOFI

Arrangements for a meeting

An anonymous, non-contactable, health professional alleged that in mid December 2011 Sanofi and Novo Nordisk (see Case AUTH/2470/1/12) had paid for what was clearly a Christmas party for the clinicians, nurses and administrative staff of a local diabetes team.

The evening meeting, which was at a local restaurant, was organised between the clinical lead consultant and the representatives involved.

The complainant stated that the supposed agenda did not materialise, that there was a partition to supposedly separate representative stands and that a representative from another company arrived but then left.

The detailed response from Sanofi is given below.

The Panel was concerned about Sanofi's submission that there was no written correspondence between its representative and the meeting organiser and considered that companies sponsoring meetings organised by a third party had to satisfy themselves that all of the arrangements, including the agenda, venue and invitation, complied with the Code. It was difficult to understand why and how, in the absence of any written documentation, the company decided that it was an appropriate meeting to sponsor given that it was an evening meeting in a restaurant held during the week prior to Christmas.

The Panel noted that, according to the agenda the meeting began at 7pm, featured two short presentations and finished with a question and answer session at 7.50pm. The six slides presented by one consultant detailed his background, clinical interests and reasons for moving to the area. The Panel queried the educational content of the presentation and whether this was a suitable presentation for the industry to sponsor.

The Panel noted that the restaurant did not charge room hire. It was unclear whether the representative had taken any steps to ensure that the venue was acceptable. The Panel noted that whilst the floor plan sketch indicated a degree of separation between the public part of the restaurant and the meeting, the arrangements were not such as to constitute a private room and the Panel queried whether in that regard the arrangements were acceptable.

The total cost per head for the evening, to include drinks, was £32.81. Sanofi paid £503.15 but did not provide a credit card receipt.

Overall the Panel was very concerned about the impression given by the arrangements. It was extremely important that representatives controlled the arrangements for meetings which they sponsored. There had been no more than 1 hour of education and overall the evening appeared to be primarily a Christmas social event; there was no documentary evidence that the meeting complied with the Code. A breach of the Code was ruled which was appealed by Sanofi. The Panel considered that the representative had failed to maintain high standards. A breach of the Code was ruled which was not appealed.

The Panel was extremely concerned that there was no written communication about the meeting arrangements given its date, time and the absence of a private room. Although the meeting was initiated and organised by a local clinician, it was beholden upon the company to check that all of the arrangements were consistent with the Code and in the Panel's view the company had not met its obligations in this regard. None of the meeting material before the Panel contained a declaration of the company's sponsorship. The Panel considered that, overall, the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed by Sanofi.

The Appeal Board was concerned that Sanofi had not seen the agenda, invitation or meeting slides or checked the venue before agreeing to sponsor the meeting which had already been arranged by the organiser. The Appeal Board considered that in the absence of any written documentation it was difficult to see how the representative had decided that it was appropriate to sponsor the meeting.

The Appeal Board was disappointed to note that the representative's electronic record of the meeting had not been provided. This appeared to be the only written document which Sanofi had about the meeting arrangements. In the Appeal Board's view this should have shown the basis upon which Sanofi had agreed to support the meeting and would have provided helpful information in that regard. The Appeal Board was also concerned that Sanofi had not produced a credit card receipt showing the time that the restaurant bill was paid. The Appeal Board noted that although the meeting was jointly sponsored, Sanofi had paid more than Novo Nordisk and queried whether this meant that the Sanofi representative had stayed longer and paid for additional subsistence.

The Appeal Board considered that Sanofi had taken inadequate measures to ensure that the arrangements for the pre-organised meeting, which its representative had agreed to sponsor, complied with the Code. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its concerns above, but in light of the educational content it decided that on balance the arrangements were not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The Appeal Board ruled no breach of Clause 2. The appeal on this point was successful.

An anonymous, non-contactable, health professional complained about a meeting sponsored by Sanofi and Novo Nordisk Limited (see Case AUTH/2470/1/12) in December 2011 which had taken place at a local restaurant.

COMPLAINT

The complainant was concerned at the blatant disregard by a pharmaceutical company to ethics when promoting medicines. The complainant alleged that in December 2011 Novo Nordisk and Sanofi had paid for what was clearly a Christmas party for the clinicians, nurses and administrative staff of a local diabetes team.

The meeting, which the complainant considered was a party, had been organised amicably between the clinical lead consultant and the representatives involved.

The complainant stated that there was a supposed agenda but this did not materialise, that there was a partition to supposedly separate representative stands and that a representative from another company arrived but then left. Diabetes therapy in the trust consisted predominantly of Novo Nordisk products.

When writing to Sanofi, the Authority asked it to consider the requirements of Clauses 2, 9.1, 15.2 and 19.1 of the 2011 Code as the meeting took place in 2011.

RESPONSE

Sanofi submitted that a consultant diabetologist had asked one of its field sales managers to support a meeting entitled 'Diabetes Bringing Teams Together'. The meeting was arranged in light of personnel changes within the trust and a review of diabetes services. It was due to run for an hour with two talks, both by diabetes consultants, entitled 'Diabetes in the [local area]' and 'Bringing Teams Together' followed by a question and answer session. The meeting ran for 1 hour 40 minutes. There were neither company personnel presentations nor a stand at the meeting.

The meeting was attended by one of Sanofi's sales team and twenty five delegates (including the meeting chair and the two presenters). The delegates comprised three consultant diabetologists, three podiatrists, two dieticians, nine nurses, three registrars, two GPs and three diabetes secretaries. Four other health professionals were invited but did not attend. The invitations were sent out by the consultant diabetologist who arranged the meeting.

The hospitality costs were split with Novo Nordisk. Sanofi paid £503.15 which was approximately half the bill for food and drink at the meeting. The hospitality consisted of thirty pre-booked set meals (hence the difference between the number of delegates and number of meals) at £24.95 with the remainder for drinks.

Sanofi submitted that two letters it had received, from the meeting organiser and from one of the consultant speakers, made the educational content and nature of the meeting clear. The letters thanked Sanofi for its financial support to enable the meeting to happen. Sanofi stated that it was clear from the letters that this was a bona fide educational meeting and not a Christmas party as alleged.

Sanofi was confident that the meeting was carried out in accordance with the Code; there was no promotional content and it had a substantial educational component and therefore it was not inappropriate for it to be sponsored. The hospitality provided was at an appropriate level. Documents outlining the arrangements documented this accurately. Sanofi considered that high standards had been maintained throughout, and did not accept that any breach of Clauses 2, 9.1, 15.2 or 19.1 had occurred.

In response to the case preparation manager's request for further information, Sanofi submitted that the letters from the meeting organiser and one of the speakers had been received after it received the complaint when it contacted the two individuals concerned for their views of the meeting. There was no written correspondence between the representative and the meeting organiser and the representative had passed the ABPI Medical Representatives Examination.

In response to the Panel's request for further information, Sanofi explained that the information upon which the decision was made to sponsor the meeting was that given during the meeting between the meeting organiser and representative. It was considered that this meeting was appropriate to sponsor as the field team had worked with the department, along with several other companies, throughout the year as it reviewed its diabetes service and attempted to find a more integrated way of working with primary care; it had just appointed two new consultants from outside the area and the meeting, which was non-promotional, was about organisational change.

The meeting invitation (of which Sanofi did not have a copy) was sent by the meeting organiser and not by the representative. A copy of the agenda which was used on the night was provided.

The meeting took place in a part of the restaurant which was clearly separate from the public part of the restaurant and no members of the public entered the area in which the presentations were taking place. A sketch of the restaurant's floor plan was provided.

A copy of the presentation by one of the consultants was provided. Sanofi did not have a copy of the second presentation but noted that it had been obtained and provided by Novo Nordisk.

PANEL RULING

The Panel noted that the Code permitted companies to provide hospitality within certain parameters as set out in Clause 19.1 which stated that 'The level of subsistence offered must be appropriate and not out of proportion to the occasion. The costs involved must not exceed that level which the recipients would normally adopt when paying for themselves'. The Panel also noted the supplementary information to Clause 19.1, Meetings and Hospitality, which set out certain basic principles for any meeting: the meeting must have a clear educational content, the hospitality associated with the meeting must be secondary to the nature of the meeting and must be appropriate and not out of proportion to the occasion and that any hospitality provided must not extend to spouses and other persons unless that person qualified as a proper delegate or participant at the meeting in their own right. Administrative staff might be invited to meetings where appropriate. The venue must be appropriate and conducive to the main purpose of the meeting. Further, the Panel noted that the supplementary information also stated that 'The impression that is created by the arrangements for any meeting must always be kept in mind'. In addition, the Panel considered that as a principle representatives sharing the cost of a meeting would not make otherwise excessive costs acceptable under the Code.

The Panel was concerned about Sanofi's submission that there was no written correspondence between its representative and the meeting organiser. The Panel considered that companies sponsoring meetings organised by a third party had to satisfy themselves that all of the arrangements, including the agenda, venue and invitation, complied with the Code. It was difficult to understand why and how, in the absence of any written documentation, the company decided that it was an appropriate meeting to sponsor given that it was an evening meeting in a restaurant held during the week prior to Christmas.

The Panel noted that, according to the agenda the meeting began at 7pm and featured two short presentations; 'Diabetes Towards a Sweet Future' (20 minutes) and 'Diabetes in the [local area] – Why Here?' (15 minutes) and finished with a question and answer session at 7.50pm. The six slides presented detailed his background, clinical interests and reasons for moving to the area. The Panel queried the educational content of the presentation and whether this was a suitable presentation for the industry to sponsor.

The Panel noted that the meeting took place in a restaurant. No room hire was charged. It was unclear whether the representative had taken any steps to ensure that the venue was acceptable. The Panel noted that whilst the floor plan sketch indicated a degree of separation between the public part of the restaurant and the meeting, the arrangements were not such as to constitute a private room and the Panel queried whether in that regard the arrangements were acceptable.

The cost of the meal was £24.95 per head and including drinks the total cost of the evening was £953.15 (including the cost of four meals for non-attendees), of which Sanofi bore £503.15. The total cost per head for the evening was £32.81. Sanofi did not provide a credit card receipt.

Overall the Panel was very concerned about the impression given by the arrangements. It was extremely important that representatives controlled the arrangements for meetings which they sponsored. There had been no more than 1 hour of education and the overall arrangements implied that the evening was primarily a Christmas social event. The company had sponsored an evening event which was held in a restaurant 10 days before Christmas with no documentary evidence that it complied with the Code. A breach of Clause 19.1 was ruled. This ruling was appealed by Sanofi. The Panel considered that the representative had failed to maintain high standards. A breach of Clause 15.2 was ruled. The Panel considered that the alleged breach of Clause 9.1 was covered by its ruling of a breach of Clause 15.2.

The Panel was extremely concerned that there was no written communication about the meeting arrangements given its date, time and the absence of a private room. Irrespective of the fact that it was initiated and organised by a local clinician, it was beholden upon the company to check that all of the arrangements were consistent with the Code and in the view of the Panel the company had not met its obligations in this regard. None of the meeting material before the Panel contained a declaration of the company's sponsorship as required by Clause 19. The Panel considered that, overall, the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed by Sanofi.

APPEAL BY SANOFI

Sanofi noted that the complainant stated that the meeting was 'a Christmas party', but provided no description of the event beyond this, nor any substantive comment as to why the content was not educational. Although the complainant also referred to a '… blatent disregard … to ethics when promoting medicines', Sanofi submitted that the evidence showed that the meeting was entirely educational with no promotion occurring (either through direct presentation or through the presence of promotional stands/materials).

Sanofi noted that the supplementary information to Clause 19.1 stated that 'the meeting must have a clear educational content'. Sanofi submitted that it was not true to state that the meeting did not have educational content. The agenda for the meeting gave a clear indication that the topic for consideration was effective team working and local service provision, and this was an essential consideration if healthcare was to be delivered effectively. It was clear from one of the consultant's slides that there was content around service provision in the region and this constituted suitable content for a company-sponsored educational meeting.

Sanofi submitted that the presentations and discussions lasted for 1 hour 20 minutes which was a reasonable amount of time to then provide some hospitality. The hospitality provided was reasonable and in line with what the attendees might expect to pay for themselves. Although the meeting was held in December this was a normal working period for the health service and Sanofi considered the date of the meeting irrelevant in this case given that there was clear educational content.

In summary, Sanofi submitted that the meeting had educational content and therefore in light of the reasonable hospitality provided it did not constitute a breach of Clause 19.1.

Sanofi did not accept that the meeting breached Clause 19.1 and as such did not accept that the arrangements for the meeting brought the industry into disrepute.

APPEAL BOARD RULING

The Appeal Board was concerned that Sanofi had not seen the agenda, invitation or meeting slides or checked the venue before agreeing to sponsor the meeting which had already been arranged by the organiser. The Appeal Board considered that in the absence of any written documentation it was difficult to see how the representative had decided that it was appropriate to sponsor the meeting.

The Appeal Board was disappointed to note that a copy of the representative's entry into the company's customer relations management (CRM) system had not been provided. This appeared to be the only written document which Sanofi had about the meeting arrangements. In the Appeal Board's view this entry should have shown the basis upon which Sanofi had agreed to support the meeting and would have provided helpful information to the Appeal Board in that regard. The Appeal Board was also concerned to note that Sanofi had not produced a credit card receipt showing the time that the restaurant bill was paid. The Appeal Board noted that although the meeting was jointly sponsored, Sanofi had paid more than Novo Nordisk and queried whether this meant that the Sanofi representative had stayed longer and paid for additional subsistence.

The Appeal Board considered that Sanofi had taken inadequate measures to ensure that the arrangements for the pre-organised meeting, which its representative had agreed to sponsor, complied with the Code. The Appeal Board upheld the Panel's ruling of a breach of Clause 19.1 of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its concerns above, but in light of the educational content it decided that on balance the arrangements were not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The Appeal Board ruled no breach of Clause 2. The appeal on this point was successful.

Complaint received **3 January 2012**

Case completed **14 May 2012**

CASE AUTH/2472/1/12

SHIRE v FLYNN PHARMA

Medikinet leavepiece

Shire Pharmaceuticals complained about a Medikinet XL (methylphenidate prolonged release) leavepiece issued by Flynn Pharma. Medikinet was indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when remedial measures alone proved insufficient.

Shire noted that the second page of the leavepiece (headed 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles') featured plasma concentration-time curves from two comparative pharmacokinetic studies conducted in adults (Equasym XL vs Medikinet XL (Schütz *et al* 2009) and Equasym XL vs Concerta XL (González *et al* 2002)). There was no contextual information about the relevance of these comparative studies to the treatment of ADHD in children or any comment on the clinical significance of the data. Shire alleged that the graphs, with Equasym XL as the common comparator, invited readers to extrapolate a favourable but misleading comparison between the pharmacokinetic profiles of Medikinet XL and Concerta XL, when in fact there were no data to support this.

The front page of the leavepiece set the clinical question 'How do you achieve a good start to the day for children and adolescents with severe ADHD who are hyperactive and/or inattentive at the start of the school day?' and proposed Medikinet and Medikinet XL as the answer with only comparative pharmacokinetic data from adult studies to support it. Shire alleged that this presentation of adult pharmacokinetic data breached the Code as it was misleading and did not enable readers to form a rational opinion of the therapeutic value of Medikinet XL.

Shire alleged a further breach as the inclusion of comparative adult pharmacokinetic data implied that Medikinet XL had a superior clinical profile compared with Equasym XL and Concerta XL although no clinical studies had shown this to be so.

The detailed response from Flynn is given below.

The Panel noted that the front page of the leavepiece posed the question 'How do you achieve a good start to the day for children and adolescents with severe ADHD who are hyperactive and/or inattentive at the start of the school day?' Page 2 was headed 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles' and featured two graphs which showed the mean methylphenidate plasma concentration-time profiles in healthy adult volunteers for three different medicines. The first graph (Medikinet XL 20mg vs Equasym XL 20mg (adapted from Schütz *et al*)) clearly showed that at 2 hours post-dose, Medikinet XL 20mg achieved higher methylphenidate plasma concentrations than Equasym XL 20mg. The second graph (Equasym XL 20mg vs Concerta XL 18mg (adapted from González *et al*)) also showed that 2 hours post-dose, Equasym XL 20mg achieved higher methylphenidate plasma concentrations than Concerta XL 18mg.

In the Panel's view, the graphs encouraged readers to compare the plasma concentration-time profiles of Medikinet XL, Equasym XL and Concerta XL and concluded that, in the first few hours post-dose, Medikinet XL achieved a higher methylphenidate plasma concentration than the other medicines. In that regard the Panel considered that some readers might assume that this resulted in a clinical advantage for children who were hyperactive and/or inattentive at the start of a school day thus answering the question posed on the front page of the leavepiece.

The Panel noted that although the leavepiece did not refer to any clinical data, it did not state that the depicted pharmacokinetic differences in healthy adult volunteers had not been shown to have consequential differences in clinical outcome when used to treat ADHD in children. The Panel noted Shire's submission that there were no clinical studies to show that Medikinet XL had a superior clinical profile to either Equasym XL or Concerta XL.

The Panel considered that the presentation of the pharmacokinetic data was such that the comparisons of Medikinet XL with Equasym XL and Concerta XL were misleading as alleged. A breach of the Code was ruled.

Shire Pharmaceuticals Limited complained about a four page, A5 Medikinet XL (methylphenidate prolonged release) leavepiece (ref MXL/LVP/11/0038) issued by Flynn Pharma Limited. Medikinet was indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when remedial measures alone proved insufficient. Shire marketed Equasym XL (methylphenidate prolonged release) for the same indication.

COMPLAINT

Shire alleged that use of adult pharmacokinetic data in the leavepiece was misleading. During inter-company dialogue Flynn submitted that the leavepiece had been withdrawn but did not accept Shire's arguments in relation to the pharmacokinetic data, and provided no reassurance that similar claims and graphs would not be used in future material.

Shire noted that the second page of the leavepiece (headed 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles') featured graphs of plasma concentration-time curves from two comparative pharmacokinetic studies conducted in adults (one comparing Equasym XL and Medikinet XL (Schütz *et al* 2009), and the other comparing Equasym XL and Concerta XL [methylphenidate marketed by Janssen Cilag] (González *et al* 2002)). There was no contextual information provided about the relevance of these comparative studies to the treatment of ADHD in children or indeed any comment on the clinical significance of the data. There was no discussion or presentation of any therapeutic studies comparing these products. In the absence of any explanatory text or guidance Shire alleged that the graphs, with Equasym XL as the common comparator, invited readers to extrapolate a favourable but misleading comparison between the pharmacokinetic profiles of Medikinet XL and Concerta XL, when in fact there were no data to support this.

Shire alleged that this was compounded by the fact that the only part of the leavepiece that provided any information about the clinical performance of Medikinet XL was the statement on the opposite page (page three) that the release profile had been designed to mimic two equal doses of methylphenidate given four hours apart.

Shire alleged that this presentation of adult pharmacokinetic data was in breach of Clause 7.2. This clause required that promotional material was not misleading and that it was sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine. The front page of the leavepiece set the clinical question 'How do you achieve a good start to the day for children and adolescents with severe ADHD who are hyperactive and/or inattentive at the start of the school day?' and proposed Medikinet and Medikinet XL as the answer. However, it provided only comparative pharmacokinetic data from adult studies to support this. Shire considered that this was misleading and did not enable readers to form a rational opinion of the therapeutic value of Medikinet XL.

Shire further alleged that this presentation of data was in breach of Clause 7.3 which allowed comparisons provided they were not misleading. The inclusion of comparative adult pharmacokinetic data implied that Medikinet XL had a superior clinical profile compared with Equasym XL and Concerta XL. However, no clinical studies had shown this to be so.

Shire submitted that it had consistently maintained that the presentation of pharmacokinetic differences between products in a manner which inferred a clinical difference was misleading. In particular, Shire disagreed with Flynn's continued assertion that it was acceptable to use comparative pharmacokinetic data from healthy, adult volunteers to highlight differences between Medikinet XL and Equasym XL for use in children and adolescents with ADHD. Shire did not consider Flynn's presentation of pharmacokinetic data was acceptable or legitimate and had clearly stated its position in inter-company dialogue in relation to the leavepiece and similar previous items.

RESPONSE

Flynn submitted that both Shire and the PMCPA, in its letter notifying Flynn of the complaint, acknowledged that the leavepiece had been voluntarily withdrawn and to this extent Flynn understood that inter-company dialogue had been successful. The basis and the subject of the complaint was thus not entirely clear. The leavepiece at issue had been withdrawn and was pending revision. However, the same information was used in a Medikinet detail aid that was pending revision. A copy of the draft detail aid was provided. It had not yet been approved for use, however the presentation of pharmacokinetic data was essentially the same as that in the leavepiece at issue.

Flynn submitted that whilst Shire's complaint about the presentation of pharmacokinetic data characterised the issues as the absence of contextual information provided about the relevance of these comparative studies to the treatment of ADHD in children, or indeed any comment at all on the significance of these data, Shire's letter to Flynn during inter-company dialogue stated 'you continue to believe and repeatedly assert that the use of adult pharmacokinetic data in the leavepiece is balanced and not misleading' and that 'we disagree with your argument that it is acceptable to use comparative pharmacokinetic data from healthy adult volunteers to highlight differences.... in children and adolescents'. Flynn thus queried whether it was the use of adult pharmacokinetic data *per se* that Shire took issue with, and/or the absence of any comment as to its significance.

In inter-company dialogue in 2010 about a different leavepiece, Shire commented on the use of the pharmacokinetic data now at issue. Specifically, Shire had complained about the claim that Medikinet XL had a higher bioavailability than Equasym XL which was based on Schütz *et al*. Shire had stated that the clinical relevance of this finding to the treatment of children with ADHD was unknown but that there was a clear implication that the pharmacokinetic difference was clinically relevant. In later correspondence about the use of the same data, Shire had agreed there was no clinical comparator data for Medikinet XL and Equasym XL and that pharmacokinetic data and understanding of pharmacodynamics was both intuitive and important. Flynn submitted that it found the situation somewhat perverse – whereas previously Shire had objected to any inference or suggestion as to the significance or clinical meaning of pharmacokinetic data (a complaint Flynn accepted and took into full consideration in the production of the leavepiece now at issue), Shire now objected to the absence of such an extrapolation.

Flynn submitted that in inter-company dialogue Shire had emphatically challenged the use of adult pharmacokinetic data whereas now it challenged the

absence of contextual information where such data were used. Flynn submitted that Shire had previously questioned the use of contextual information, to which Flynn responded by its removal. What was it to be?

Flynn submitted that González *et al* reported a study of methylphenidate bioavailability from two extended-release formulations (Equasym XL and Concerta XL). The study was sponsored by Celltech and three of the authors were employees of that company. Celltech (UCB) was the original developer and licence holder for Equasym XL before divesting rights to Shire. Pharmacokinetic data from González *et al* was reproduced as one of the two graphs in the leavepiece at issue. The study was clearly referenced and relied on Gonzalez *et al* by way of supporting information. The 'Discussion and conclusions' section of Gonzalez *et al* stated:

> 'The objective of these studies was to compare the rate and extent of MPH [methlyphenidate] absorption from single doses of two extended-release MPH formulations. Whilst both formulations contain an immediate release as well as extended release MPH components, **it is important for clinicians to be aware of the similarities and differences in the plasma profile** resulting from dosing of these formulations….' (emphasis added)
>
> 'The majority of ADHD patients that receive MPH treatment are children or adolescents. However, we chose adult subjects for these studies because of ethical considerations regarding the enrolment of children into clinical studies that involve invasive procedures with little expectation of clinical benefit. Despite the limitation, we believe the results presented have potential significance for children and adolescents. Thus, although the absolute plasma levels of MPH resulting from any given dose are generally higher in children than adults – most likely due to differences in dose-weight ratio – **the pharmacokinetic profiles of MPH in adults and children are qualitatively similar and there are no age-related differences in absorption, distribution, metabolism or excretion of MPH**.' (emphasis added)

Flynn submitted, and considered it was entirely supported by Gonzalez *et al*, that it was entirely reasonable and justified to make use of adult pharmacokinetic data in these circumstances.

However, during inter-company dialogue, Shire strongly challenged the use of adult pharmacokinetic data. Flynn found the position disingenuous if not duplicitous given than Shire also used adult pharmacokinetic data in the same therapy area. In its leavepiece, a whole page was devoted to presentation of the same González *et al* pharmacokinetic comparison of Concerta XL and Equasym XL under the heading 'Equasym XL delivers higher plasma concentrations versus Concerta XL during the early part of the school day'. In a later leavepiece Shire took a further step, albeit backwards in Flynn's view, in making claims of clinical relevance in connection with a statement as to Equasym XL's 'unique dose-ratio designed to make the most of the school day'. In that case the ratio referred to (30/70 immediate/delayed release components) was a reference to the pharmaceutical *in vitro* release of methylphenidate. Notwithstanding, Shire seemed comfortable to extrapolate to the clinical situation.

Flynn suggested that, for the purposes of argument however, it accepted that the use of adult pharmacokinetic data in this therapy area was meaningful and acceptable. Flynn was then left to consider the alleged breach of Clause 7.2 on the grounds that the presentation of both González *et al* and Schütz *et al* pharmacokinetic data in separate graphs was misleading and invited readers to extrapolate a favourable (but misleading) comparison between the pharmacokinetic profiles of Medikinet XL and Concerta XL. Flynn submitted that this was patently not the case and required readers to make a lateral jump in thinking that, in Flynn's view, they would not make. These were two separate published pharmacokinetic comparisons of two products in each, and Equasym XL was common to both studies. Shire asked Flynn to believe that readers might extrapolate a favourable but misleading comparison between Medikinet XL and Concerta XL. Flynn submitted that the audience, informed and expert child psychiatrists and paediatricians, was more than familiar with the therapy area, the use of stimulants and the extensive literature describing pharmacokinetic and pharmacodynamics correlation. In particular, they would not be misled or accept a suggested or claimed clinical advantage of one product over another based only on pharmacokinetic differences. Further, they would not naturally be drawn to superimpose in their mind's eye the two graphs. The two graphs were given equal prominence, were clearly and separately referenced (as originating from two different studies) and were presented in such a way as to invite readers to consider the two pieces of information separately. They were presented in the context of the heading of 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles'. Flynn submitted that similarly, on the opposite page, it presented information on the *in vitro* release profiles and product pricing for the three different extended release preparations. Flynn considered the piece was a balanced presentation of salient differences between the products in terms of pharmacokinetics, pharmaceutics and price.

Flynn therefore denied the alleged breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that although the leavepiece at issue had been withdrawn as a result of successful inter-company dialogue on other matters raised by Shire, the same pharmacokinetic information was to be used in a Medikinet detail aid which was currently under revision. In that regard there appeared to be a clear intent to continue using the data. The Panel therefore considered that inter-company dialogue in relation to the use of this data had been unsuccessful.

The Panel noted that the front page of the leavepiece posed the question 'How do you achieve a good start to the day for children and adolescents with severe ADHD who are hyperactive and/or inattentive at the start of the school day?' Page 2 was headed 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles' and featured two graphs which compared the mean methylphenidate plasma concentration-time profiles in healthy adult volunteers for Medikinet XL 20mg and Equasym XL 20mg (adapted from Schütz *et al*) and for Equasym XL 20mg and Concerta XL 18mg (adapted from González *et al*). The Panel noted that the first graph clearly showed that at 2 hours post-dose, Medikinet XL 20mg achieved higher methylphenidate plasma concentrations than Equasym XL 20mg. The peak plasma concentration achieved with Medikinet (4½ hours post-dose) was just under 4.5ng/ml.

The second graph (adapted from González *et al*) compared the plasma concentration-time curves for Equasym XL 20mg and Concerta XL 18mg. The results from this study showed a slightly different plasma concentration-time profile for Equasym XL compared with the results reported by Schütz *et al*, nonetheless the graph showed that 2 hours post-dose, Equasym XL 20mg achieved higher methylphenidate plasma concentrations than Concerta XL 18mg (approximately 3ng/ml and 2ng/ml, respectively). Peak plasma levels for Concerta (approximately 3.7ng/ml) were not achieved until 6 hours post-dose.

The Panel disagreed with Flynn's submission that readers would not be drawn to superimpose in their mind's eye the two graphs. The graphs were positioned next to each other, and both used Equasym XL as the comparator. The dosage of Equasym XL used in both studies was 20mg and the line depicting the plasma concentration of methylphenidate for Equasym XL was the same colour in each graph. In the Panel's view, the graphs encouraged readers to compare the plasma concentration-time profiles of Medikinet XL, Equasym XL and Concerta XL and conclude that, in the first few hours post-dose, Medikinet XL achieved a higher methylphenidate plasma concentration than the other medicines. In that regard the Panel considered that some readers might assume that this resulted in a clinical advantage for children who were hyperactive and/or inattentive at the start of a school day thus answering the question posed on the front page of the leavepiece.

The Panel considered that whilst readers might find pharmacokinetic data useful, care must be taken not to present such data in a way which implied consequential clinical benefit unless a direct link between the two had been established. The Panel noted that the data depicted was from healthy adult volunteers and that the absolute plasma levels of methylphenidate resulting from any given dose were generally higher in children than adults. This was not stated in the leavepiece nor was any indication given of the methylphenidate plasma concentration needed for a therapeutic effect in ADHD in children.

The Panel noted that although the leavepiece did not refer to any clinical data, it did not state that the depicted pharmacokinetic differences in healthy adult volunteers had not been shown to have consequential differences in clinical outcome when used to treat ADHD in children. The Panel noted Shire's submission that there were no clinical studies to show that Medikinet XL had a superior clinical profile to either Equasym XL or Concerta XL.

The Panel considered that the presentation of the pharmacokinetic data was such that readers would not be able to understand the significance of the data or form their own opinion of the therapeutic value of Medikinet XL vs Equasym XL or Concerta XL. A breach of Clause 7.2 was ruled. The comparisons of Medikinet XL with Equasym XL and Concerta XL were misleading as alleged in that regard. A breach of Clause 7.3 was ruled.

Complaint received **11 January 2012**

Case completed **22 February 2012**

CASE AUTH/2473/1/12

VOLUNTARY ADMISSION BY VIFOR

Ferinject advertisement

Vifor Pharma advised the Authority that three advertisements for Ferinject (ferric carboxymaltose) solution for injection/infusion, placed in international journals by its global colleagues, had not been certified in accordance with the Code. Ferinject was indicated for the treatment of iron deficiency when oral iron preparations were ineffective or could not be used.

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

The detailed response from Vifor is given below.

The Panel noted Vifor's submission that the content of each journal was produced in the UK for a European and international circulation. Vifor submitted that the editorial offices for each of the three journals was managed from, and the journals were typeset and printed in, the UK. The Panel thus considered that the advertisements in the journals at issue fell within the scope of the Code.

The Panel noted that although the advertisements for Ferinject had been placed by Vifor's global office, it was an established principle that UK companies were responsible for the acts/omissions of overseas parents and affiliates that came within the scope of the Code. The advertisements had not been certified in accordance with the UK Code. The Panel thus ruled a breach of the Code in relation to each advertisement, as acknowledged by Vifor.

Vifor Pharma Limited made a voluntary admission in relation to three advertisements for Ferinject (ferric carboxymaltose) solution for injection/infusion placed in international journals by its global colleagues. Ferinject was indicated for the treatment of iron deficiency when oral iron preparations were ineffective or could not be used.

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

COMPLAINT

The three advertisements at issue were organised by Vifor's global colleagues and were signed off globally, but were not certified in accordance with the Code. The advertisements were placed in the following journals:

- European Journal of Heart Failure, January 2012 (artwork placed 28 November 2011)
- European Heart Journal, December 2011 (artwork placed 3 November 2011)
- NDT (Nephrology Dialysis Transplantation), December 2011 (artwork placed 11 November 2011)

Vifor submitted that the journal content was produced in the UK for European and international circulation including UK circulation. The journals were not aimed exclusively at a UK audience, however they were printed in English and produced by a UK publisher.

Vifor submitted that as soon as the advertisements came to its attention it arranged meetings with its global colleagues. The global teams were trained on the Code in December 2011 and were now well aware of their responsibilities in certifying advertisements placed in journals that were produced, published and directed towards the UK. The advertisements in question were placed before the December training session.

Vifor submitted that these corrective actions had been taken to avoid a repetition of such instances. In addition processes had been revisited to ensure there were correct procedures to ensure that global teams followed the certification process when they initiated these advertisements in the future.

When writing to Vifor, the Authority asked it to respond in relation to Clauses 1.1 and 14.1 of the Code and drew attention to the supplementary information to Clause 1.1, Journals with an International Distribution.

RESPONSE

Vifor reiterated that the journal content was produced in the UK for European and international circulation including UK circulation. Each advertisement contained the international strapline 'Mastering the art of iron therapy' that was ruled in breach in Case AUTH/2411/6/11 [the correct case number was AUTH/2423/7/11]. The journals were not aimed at UK health professionals exclusively however they were in English and produced by a UK publisher. Production and circulation details for the journals were provided.

Vifor UK trained the global teams as soon as the breach of the Code came to its attention. The global teams were trained in December and were now fully aware of the responsibilities the UK and all affiliates had when distributing material within the UK and in particular the requirements to certify advertisements placed in journals produced, published and directed towards the UK. Furthermore, a comprehensive list of journals had been provided to the global teams indicating which would require future review by Vifor in the UK.

Vifor submitted that in addition to the training, internal processes for Vifor's global teams had been revised to take in to account the need for UK certification and avoid similar situations in the future.

In response to a request for further information, Vifor submitted the editorial offices for the three journals at issue were managed through the UK, the journals were typeset in Salisbury and printed in Glasgow.

With respect to the steps taken to communicate the ruling in Case AUTH/2411/6/11 [the correct case number was AUTH/2423/7/11] in relation to the strapline used in the advertisements at issue, Vifor submitted that when it became aware that a Ferinject advertisement had appeared in the NDT Journal, it immediately notified its global colleagues and reiterated the importance of having all journal advertisements certified in accordance with the Code. On 10 January Vifor informed the Authority that an investigation was on-going to determine if any other advertisements had been placed in any other journals. Several telephone conversations and emails were exchanged between Vifor, global marketing and global medical departments in order to identify all advertisements that were placed without Vifor certification. The three advertisements in question were identified and highlighted to the Authority on 20 January. A definitive list identifying which journals required Vifor certification before placement of an advertisement was finalised between global and Vifor on 20 January.

In response to a request for further information, Vifor provided a copy of an email it had sent on 19 August 2011 to global colleagues about the ruling in Case AUTH/2423/7/11.

PANEL RULING

The Panel noted that it had to consider as a preliminary issue whether advertisements in the journals in question came within the scope of the Code. The supplementary information to Clause 1.1, Journals with an International Distribution, stated that the Code applied to the advertising of medicines in professional journals which were produced in the UK and/or intended for a UK audience. The identification of the country in which a journal was 'produced' was based on factors such as where it was compiled and edited, and where it was typeset, printed and bound, rather than on factors such as the location of the head office of the publisher.

The Panel noted Vifor's submission that the content of each journal was produced in the UK for a European and international circulation. Vifor had submitted that the editorial offices for each were managed through the UK publisher and that the journals were typeset in Salisbury and printed in Glasgow. The Panel therefore considered that the advertisements in these journals fell within the scope of the Code.

The Panel noted that although the advertisements for Ferinject had been placed by Vifor's global office, it was an established principle that UK companies were responsible for the acts/omissions of overseas parents and affiliates that came within the scope of the Code. The advertisements had not been certified in accordance with the UK Code. The Panel thus ruled a breach of Clause 14.1 in relation to each advertisement, as acknowledged by Vifor.

During the consideration of this case the Panel was extremely concerned to note that the advertisements at issue featured the strapline 'Mastering the art of iron therapy' which was ruled in breach of Clause 7.2 of the Code in Case AUTH/2423/7/11. Vifor had accepted the ruling and had signed the relevant undertaking and assurance in August 2011. Subsequent placement of advertisements with the same strapline was therefore potentially in breach of that undertaking. The Panel noted that Vifor had voluntarily admitted a breach of the Code with regard to certification but not with regard to a breach of undertaking. The Constitution and Procedure did not permit the Panel to consider matters which were not the subject of a complaint or voluntary admission and thus it could not rule on this matter. Nonetheless, the Panel noted that a breach of undertaking was a very serious matter and it requested that Vifor be advised of its concerns in that regard.

Complaint received **24 January 2012**

Case completed **23 March 2012**

ANONYMOUS v ALLERGAN

Conduct of employees

The Authority received an anonymous complaint from non-contactable complainants about the conduct of two Allergan employees at the Merz symposium at the International Master Course on Aging Skin (IMCAS) meeting held in Paris, January 2012.

The complainants stated that they were disgusted by the behaviour of two members of Allergan's staff whom they alleged had to be thrown out of the Merz symposium for repeatedly taking photographs and recording the session despite signs and requests from the chairman not to do so. The complainants stated that they were particularly upset to hear one of the employees subsequently boasting and laughing about the incident in the hotel foyer.

The detailed response from Allergan is given below.

The Panel noted that the complainants were anonymous and non-contactable and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and, like all complaints, judged on the evidence provided by the parties. The Panel also noted the difficulty of dealing with complaints based on one party's word against the other.

The Panel noted that Allergan's recollection of the event at issue differed from that of the complainants'. Allegan had submitted that the two employees in question had attended IMCAS for its educational value and to aid their continuing professional development. Both had attended the Merz symposium and had taken photographs during the symposium. The Panel noted Allegan's submission that neither employee was aware of a sign or statement by the chairman that photographs could not be taken. The Panel also noted that staff facilitating the meeting had asked the employees in question to delete any photographs, which they did and then left the symposium. Both employees denied discussing the matter in the hotel lobby.

The Panel was concerned that there was no written brief or instructions on conduct for UK based Allegan employees when attending a meeting on behalf of the company, but considered that there was no evidence submitted by the complainants to indicate that Allegan or its employees had failed to maintain high standards. No breach of the Code was ruled. The Panel noted the above ruling and Allegan's submission that neither employee was a representative and ruled no breach of the Code. The Panel consequently ruled no breach of Clause 2.

The Authority received an anonymous complaint from non-contactable complainants who described themselves as 'two ex-loyal Allergan customers' about the conduct of two Allergan Ltd employees at the Merz symposium at the International Master Course on Aging Skin (IMCAS) meeting held in Paris, January 2012.

COMPLAINT

The complainants stated that they were disgusted by the behaviour of two members of Allergan's staff who had 'to be thrown out' of the Merz symposium for repeatedly taking photographs and recording the session despite signs and requests from the chairman not to do so. The complainants submitted that a lot of Allergan staff were at the symposium and most simply took lots of notes but the two employees in question were unprofessional and arrogant.

The complainants stated that they were particularly upset to hear one of the employees boasting and laughing about the incident a couple of hours later in the hotel foyer. This behaviour was unacceptable.

The complainants stated that they were loyal Allergan customers but no more.

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

RESPONSE

Allergan explained that the IMCAS was an annual meeting dedicated to achieving the highest quality of teaching through the interface of plastic surgery and dermatology. IMCAS started in 1994, in Paris, as a congress dedicated to plastic surgeons and dermatologists. Since then, IMCAS had sought to bridge the knowledge vacuum between plastic and reconstructive surgery and dermatology, thereby generating a synergetic and mutually reinforcing interface among these two fields. This European congress was open to all involved in the field of aesthetic medicine.

Allergan submitted that no UK sales representatives or product and promotions managers attended IMCAS 2012. The two employees in question had attended IMCAS for its educational value and to aid their continuing professional development. Neither was a sales representative, and so they had not undertaken the ABPI Medical Representatives Examination.

There were no instructions/briefing for any UK based employees who attended IMCAS 2012. Although UK based, all the employees who attended had a regional role.

The Merz symposium was an open session aimed at all delegates who were registered at IMCAS. The delegates were primarily health professionals with an interest in aesthetic medicine but could be anyone who had registered as a delegate, irrespective of professional qualification. Allergan was not aware of any materials distributed prior to, or at, the symposium which referred to the expected conduct of delegates.

Both employees had been asked about this alleged incident and had provided written statements about what happened (copies were provided). In summary neither employee was aware of a sign or statement by the chairman that photographs could not be taken. A number of people had taken photographs throughout the symposium. This was apparent due to the camera flashes occurring throughout the session. One employee took a photograph of a quiz question they wanted to remember. The other took a number of photographs of 'off-label' information being presented on unlicensed indications for Bocouture (Merz's toxin), including the management of crow's feet. This matter would be taken up with the relevant regulatory body in France.

Both of the employees were 'selected' from the audience by staff facilitating the meeting and asked to delete any photographs they had; both complied immediately, deleted their photographs and left the symposium. Following the meeting Allergan found that one photograph was missed and not deleted. A copy of that photograph was provided. Allergan submitted that there were no audio or video recordings made by either employee. Both employees denied any discussion of this matter in the hotel lobby as alleged.

Allergan stated that as neither employee was a sales representative, Clause 15.2 did not apply. The company was confident that its employees had maintained high standards at IMCAS and had not brought any discredit to, or reduced confidence in, the industry. Allergan therefore denied a breach of Clauses 9.1 or 2.

PANEL RULING

The Panel noted that the complainants were anonymous and non-contactable and that, as set out in the introduction to the Constitution and Procedure, complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and, like all complaints, judged on the evidence provided by the parties. The Panel also noted the difficulty of dealing with complaints based on one party's word against the other.

The Panel was unsure whether attendees included UK health professionals or not. However the employees were based in the UK and their geographical responsibilities included the UK. In addition the Panel noted that the complaint concerned their conduct. The Panel considered that on the information available to it the matter was within the scope of the UK Code.

The Panel noted that Allergan's recollection of the event at issue differed from that of the complainants'. Allegan had submitted that the two employees in question had attended IMCAS for its educational value and to aid their continuing professional development. Both had attended the Merz symposium and had taken photographs during the symposium. The Panel noted Allegan's submission that a number of other delegates had also done so and that neither employee was aware of a sign or statement by the chairman that photographs could not be taken. The Panel also noted that staff facilitating the meeting had asked the employees in question to delete any photographs, which they did and then left the symposium. In error, one photograph was not deleted. Both employees denied discussing the matter in the hotel lobby.

The Panel was concerned that there was no written brief or instructions on conduct for UK based Allegan employees when attending a meeting on behalf of the company, but considered that there was no evidence submitted by the complainants to indicate that Allegan or its employees had failed to maintain high standards. No breach of Clause 9.1 was ruled. The Panel noted the above ruling and Allegan's submission that neither employee was a representative and ruled no breach of Clause 15.2. The Panel consequently ruled no breach of Clause 2.

Complaint received **1 February 2012**

Case completed **22 February 2012**

CASE AUTH/2477/2/12

CONSULTANT PHYSICIAN v SANOFI

Conduct of representative

A consultant physician alleged that at a hospital diabetes meeting a Sanofi representative had been unprofessional in that she disparaged Levemir (insulin detemir, marketed by Novo Nordisk Limited), and quoted unpublished evidence. The representative stated that as Levemir had recently failed a non-inferiority trial against Lantus (insulin glargine, marketed by Sanofi) there was no reason clinically why it should be prescribed.

The complainant considered this was poor conduct; there were many conflicting studies in this area and it was unacceptable for a company to make negative comments against another brand.

Lantus was for the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin was required.

The detailed response from Sanofi is given below.

The Panel noted Sanofi's submission that the representative organised the meeting to, *inter alia*, discuss the results of the recent EFFICACY trial, a direct comparison of once daily Lantus vs once daily Levemir in type 2 diabetes. The representative had not used material in her presentation.

The Panel noted that the EFFICACY trial concluded that Levemir could not be claimed non-inferior to Lantus with respect to change in HbA1c. The Panel noted Sanofi's submission that representative briefings made it clear that the EFFICACY trial formed part of a comprehensive story supporting Lantus in the treatment of type 2 diabetes, and was not a stand-alone result to be delivered in isolation. At the meeting in question, however, it appeared that this was the only study discussed with regard to Lantus and that, contrary to the briefings, it was not delivered as part of an integrated Lantus story.

The Panel noted that a key message in representatives' briefing described the EFFICACY study as a 'failed study'. A second briefing document stated that further information regarding EFFICACY 'really confirms the fact that Lantus is the superior once daily basal insulin, and should be the only choice when a once-daily insulin is needed'.

The Panel noted that a summary of the EFFICACY results presented by Sanofi to its representatives contained the subtitle 'New Ammunition – The Efficacy Study'. The fourth slide entitled 'How excited should we be about Efficacy?' provided a link to a video on YouTube of two wildly excited children opening their Christmas presents. The Panel questioned whether this video provided a balanced impression of the significance of the trial results.

Following the trial summary, representatives were instructed to practice how 'you would verbalise the messages from the Efficacy paper' and to 'Focus on the language you would use, and the type of outcomes you are hoping to achieve with different customer groups'. The Panel was extremely concerned that representatives had not been given detailed written guidance on how to describe the EFFICACY data.

The final slide of the presentation, entitled 'Lantus Key Message Summary', contained a venn diagram of three inter-locking circles labelled 'Effective HbA1c Control', 'Simplicity' and 'Reassurance for You and Your Patients', respectively. A speech bubble from the 'Simplicity' circle stated 'Lantus is the only true once daily basal insulin'.

The Panel noted that the parties' accounts of what was said at the meeting differed. It was difficult in such circumstances to determine where the truth lay. A decision had to be made on the available evidence. Sanofi submitted that the representative did not tell those present that 'there is no reason clinically why you should prescribe Levemir' nor challenge their prescribing. However, given the statement in the representatives' briefing that Lantus was the only choice when a once daily insulin was required, that the representatives were encouraged to use their own words to communicate the results of the EFFICACY 'message' and the impression given from the YouTube video, the Panel considered that, on the balance of probabilities, the representative had misleadingly implied that there was no clinical reason to prescribe Levemir. A breach of the Code was ruled. The implication could not be substantiated and a further breach of the Code was ruled. The indication for Levemir was, *inter alia*, as part of a basal-bolus insulin regimen once or twice daily depending on patients' needs, and to imply otherwise disparaged the medicine. The Panel further considered that the implication that there was no clinical reason to prescribe Levemir was also disparaging. A breach of the Code was ruled.

The representative in question had not maintained high standards and a breach of the Code was ruled. The claim in representatives' briefing that Lantus 'should be the only choice when a once-daily basal insulin is needed' advocated a course of action that was likely to be in breach of the Code. In addition the Panel noted its critical comment on the representatives' briefing materials above and considered that separately and cumulatively they advocated a course of action likely to be in breach of the Code. A breach of the Code was ruled. The Panel considered that by briefing its representatives that Lantus was the only choice when a once daily insulin was required and by failing to provide adequate written guidance to representatives on how to describe

the EFFICACY study, Sanofi had not maintained high standards and a breach of the Code was ruled.

A consultant physician complained about the conduct of a Sanofi representative at a meeting at a hospital diabetes centre on 25 January.

Sanofi marketed Lantus (insulin glargine) for the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin was required.

COMPLAINT

The complainant alleged that the representative had been unprofessional in that she disparaged Levemir (insulin detemir, marketed by Novo Nordisk Limited), and quoted unpublished evidence. The representative stated (not exact words) that Levemir had recently failed a non-inferiority trial against Lantus and so there was no reason clinically why Levemir should be prescribed.

The complainant considered this was poor conduct as there were many conflicting studies in this area; with less experience the complainant considered that she would have taken the representative at her word and perhaps been influenced not to prescribe Levemir again. The complainant considered that it was acceptable for a company to promote its brand but not by negative comments against the other brand. When the complainant tackled the representative about this she was quite sure that she stood by her word.

In a further letter, the complainant stated that the representative did not use any materials to back up her claims. The complainant challenged the representative stating that she considered it poor practice to talk negatively about a competitor brand. The representative replied that she could do this as it was factual information.

The complainant stated that the representative spent the rest of the meeting demonstrating aspects of a new [blood glucose] meter the company had developed. Following the meeting one of the senior nurses asked the representative for more information about the claim about the inferiority trial for Levemir vs Lantus and she was given a link to some research studies on the Novo Nordisk clinical trial database.

When writing to Sanofi the Authority asked it to respond in relation to Clauses 7.2, 7.4, 8.1, 9.1, 15.2 and 15.9 of the Code.

RESPONSE

Sanofi submitted that the complaint arose following a meeting held a hospital diabetes centre in January 2012 between one of its sales representatives and a group of health professionals. The meeting was set up to share some new data, to discuss and demonstrate Sanofi's new blood glucose meter and to provide an important update on a recent supply issue with one of Sanofi's products.

Sanofi submitted that the representative presented data from the EFFICACY [Effect of Insulin Detemir and Insulin Glargine on Blood Glucose Control in Subjects with Type 2 Diabetes] study recently reported by the study sponsor Novo Nordisk. The representative stated that once daily Levemir had failed to demonstrate non-inferiority compared with once daily Lantus in a recent, and yet unpublished, study. One of the health professionals present challenged this and the representative gave a factual answer based on the available evidence.

Sanofi submitted that the representative had a clear recollection of the meeting and considered that she factually presented the evidence comparing the two products and refuted the allegation that she had disparaged Levemir. Sanofi considered it was to be expected that during the course of promoting a product comparisons with other products would be made. Highlighting advantages over a competitor could not be deemed to be disparaging in this case.

The representative then went on to discuss the other topics and left the meeting. Following the meeting one of the attendees asked the representative for links to the study discussed and the representative supplied links to two publicly available websites where the results of the unpublished study could be found. Sanofi noted that the customer did not request substantiation of the claims made in the call. Had this been the case, the customer would have been provided with a copy of data on file related to the study.

Sanofi confirmed that the representative in question had passed the ABPI Representatives' Examination.

Sanofi submitted that the representative's manager had attended a number of field visits with the representative before and after the meeting in question. In his view the representative had been professional in her presentation of these data in all calls he had witnessed. Furthermore, in these calls the data in question were presented in a balanced manner. The manager considered that it would be highly unlikely for the representative's conduct to be anything other than professional or for the data to have been presented in a different way in the meeting in question.

Sanofi submitted that the EFFICACY study compared the use of Lantus and Levemir in type 2 diabetes when used once daily. Sanofi considered that it was appropriate to present these findings on the basis that this was a significant clinical question and EFFICACY was the only randomised clinical trial to have assessed the effects of the two insulins when used in this manner. The study was not given undue emphasis in the sales materials used by representatives.

Clinical relevance

Sanofi submitted that once daily use of insulins was an important clinical consideration. Clinical trial experience of the two products had typically demonstrated that Levemir could achieve similar

glycaemic control to Lantus but that this often required twice daily injection at higher doses than Lantus and resulted in a greater number of injection site reactions. These had financial and personal implications for both payer and patient.

Sanofi stated that the significance of once vs twice daily injections had similarly been recognised by the National Institute for Health and Clinical Excellence (NICE), with guidance for long-acting insulin analogues being restricted, except for specific circumstances including where 'the person needs assistance from a carer or health professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily'.

Sanofi considered that to compare the effect of the two products when used in a strictly once daily setting was therefore an important and clinically relevant concern.

Evidence base

Sanofi submitted that the nature of the evidence from the EFFICACY study was described below in full in response to the requirements of Clause 7.4 of the Code. An equally important consideration, however, was whether the use of this represented the totality of evidence available, or was unnecessarily selective.

To address this question, Sanofi searched MEDLINE (up to week 2 February 2012); 27 articles which referred to both insulins and once daily therapy were identified and once limited to 'clinical trials' 13 remained. These 13 abstracts were reviewed and after excluding one study which compared the colour of injection devices, two uncontrolled observational cohorts and three pharmacodynamics studies, seven randomised clinical trials comparing the efficacy of the two insulins were identified.

Sanofi stated that in all seven studies Levemir was used twice daily, or once or twice daily according to patient need. No study was identified in which once daily Lantus and Levemir were compared. As expected (due to the absence of publication) the EFFICACY study was not identified by the search.

Sanofi also searched the Cochrane Library and a relevant systematic review from July 2011 was identified; 'Insulin detemir versus insulin glargine for type 2 diabetes mellitus' (a copy was provided). Sanofi submitted that this review contained only four randomised clinical trials comparing the two insulins. These four trials were all identified within the MEDLINE search above, and all four included the use of Levemir twice daily. Sanofi noted that a high risk of bias which arose from this difference in dosing regimen was also recognised for each of the four studies.

Finally, and as the EFFICACY study was only identified through being reported within the National Institutes of Health clinical trial registry, Sanofi searched this to identify any other trials comparing the once daily use of Lantus and Levemir. Only one such further study was identified; 'Weight Gain, Eating Patterns, and Development of Body Composition During Initiation of Basal Insulin Therapy in Patients With Type 2 Diabetes: A Comparison of Insulin Detemir and Insulin Glargine'. Sanofi submitted that this study appeared to compare exclusive once daily use of the two insulins, although the last status report (January 2011) was that recruitment was ongoing, and given a 52 week treatment period results were therefore not available. Regardless, an assessment of glycaemic control by measurement of HbA1c was not recorded as an endpoint, so the study was unlikely to provide supporting or refuting evidence once reported.

In view of these search findings, and of the consistent results of the different methodologies, Sanofi concluded that it was highly likely that the EFFICACY study was the only trial which provided evidence comparing Lantus and Levemir when used once daily.

Emphasis within sales materials

A copy of the current electronic detail aid for Lantus was provided; the first to refer to the EFFICACY study. This had been reviewed to consider whether undue emphasis was placed on the study within the overall context of discussion about Lantus. The e-detail aid consisted of 16 sequential pages. On most pages there was the option to call up an additional page to display supporting data, such as reference details or data tables to illustrate key points in more detail.

Sanofi submitted that within the three page 'Efficacy and ease of use' section, only one page focused on the EFFICACY study, and this allowed just one extra screen of information to be called up to illustrate the primary and secondary endpoints. The EFFICACY study was one of nine trials cited in the sales material to the same level of detail, ie mentioned on at least one page and with at least one screen of further detail available.

Sanofi submitted that representative briefings (a copy was provided) made it clear that although this information was the most recent addition to the Lantus sales message, it formed part of a comprehensive story supporting the place of Lantus in the treatment of type 2 diabetes, not a stand-alone result to be delivered in isolation.

Sanofi was confident that the EFFICACY study had not been given undue prominence within either sales materials or instructions to representatives.

Substantiation and accuracy

Sanofi submitted that although it could not cite a peer-reviewed publication (which was not unexpected given the lack of a positive finding), the facts were capable of substantiation through material placed in the public domain by the study sponsor (Novo Nordisk), in accordance with the recognised principles of clinical trial disclosure. The principle reference was the clinical study report

published on Novo Nordisk's clinical trials website; this provided most of the detail to substantiate the claims made in Sanofi's materials, with the exception of the 95% confidence intervals for key endpoints (including the primary endpoint). This information was therefore supplemented by information disclosed by Novo Nordisk on one of the main public trial registries, the US National Institutes of Health ClinicalTrials.Gov site. The information disclosed there provided the 95% confidence intervals key to interpreting the findings of the study. The information contained in these two sources had been consolidated into a single Sanofi data-on-file reference, which had been examined as required by the Code. A copy was provided.

Sanofi submitted that the complainant had alleged that the representative claimed that Levemir failed to demonstrate non-inferiority compared with Lantus when used once daily. Sanofi considered it was clear from the information provided in the study report that the primary objective of the study was:

> 'To compare the efficacy of insulin detemir given once daily versus insulin glargine given once daily, both treatments in combination with metformin during 26 weeks, in subjects with type 2 diabetes inadequately controlled on metformin treatment with or without one other oral antidiabetic drug (OAD)'

And that the primary objective of the study was not met:

> 'After 26 weeks, [insulin detemir] could not be claimed non-inferior to [insulin glargine] with respect to change in HbA_{1c}'

Sanofi stated that the reason for failing to meet the test on non-inferiority was not provided in the clinical study report, although it was clear that the test that had been applied related to the two-sided 95% confidence interval for the difference in treatment effect for Levemir compared with Lantus. If the upper limit of that confidence interval was to fall below 0.4%, Levemir was to be claimed non-inferior to Lantus in terms of HbA1c with respect to a non-inferiority margin of 0.4%.

Sanofi submitted that the confidence interval for the primary endpoint was however in the information presented on ClinicalTrials.Gov. This confirmed the net mean treatment difference to be a reduction of HbA1c of 0.3003% in favour of Lantus, with a 95% confidence interval of 0.1427 to 0.4580%. This made clear that the upper limit of the 95% confidence interval crossed the 0.4% non-inferiority margin, confirming the failure of Levemir to show non-inferiority compared with Lantus. This disclosure also provided the information that the entire 95% confidence interval remained above 0% (all in favour of Lantus), ie that there was a statistically significant effect in favour of Lantus. This information, along with the key secondary endpoints, both significant and non significant, were presented as the additional page of detail from the EFFICACY study, and were all an accurate representation of the figures available in the two data sources, as reflected in the data-on-file used to support the claims.

Conclusion

Taking all these matters into consideration, Sanofi considered that although the EFFICACY study was a single study comparing the once daily use of Lantus and Levemir, it was the only study that made that comparison. This was a clinically important scenario that required evidence and the material was presented without undue emphasis in promotional materials, or with any direction in representative briefings to be presented with undue emphasis.

Sanofi also considered that all claims relating to the EFFICACY study, made both verbally by the representative and written in the sales material, were a fair and accurate interpretation of the facts available, and all were substantiated by the two sets of data disclosed by Novo Nordisk. Sanofi therefore denied any breach of Clauses 7.2 or 7.4.

Sanofi submitted that the data demonstrated that once daily Levemir failed to show non-inferiority compared with once daily Lantus in the treatment of type 2 diabetes.

Sanofi considered that the information it had provided outlined the conduct of the representative in the call and showed how the data in question were represented in sales material. Sanofi considered that it had accurately represented the data from the study which showed an advantage for Lantus and this was not disparaging. Sanofi denied a breach of Clause 8.1.

A copy of all representative briefing material related to the use of the EFFICACY study was provided. Sanofi submitted that representatives were first briefed about this study in October 2011 to enable them to respond to customer enquiries. They were briefed again in December and given a pre-recorded presentation of the data to enable them to proactively discuss these new data with customers. The representatives were trained again when they received the e-detail aid referred to above.

During the course of its investigation Sanofi had identified that, regrettably, one presentation to the sales team had not been certified. It was submitted into the review process and had been reviewed and approved by two final signatories but the formal certification step was not completed. Sanofi thus accepted a breach of Clause 15.9 in relation to this one item and with that a Clause 9.1.

In light of the evidence presented above related to the meeting, Sanofi denied a breach of Clause 15.2.

Following a request for further information, Sanofi submitted that the representative in question had set the agenda for the meeting, to include new Lantus/Levemir comparative data, a demonstration of Sanofi's new blood glucose meters and an update on the supply situation of another Sanofi product. On opening the call the representative explained that

the basis of the new data was that Levemir had failed to meet non-inferiority in a trial against Lantus. The flow of the intended call was then stopped by the complainant who stated 'You are not allowed to use the words inferior and non-inferior. You should be saying superior to…'. Sanofi submitted that there was no question from the complainant for the representative to respond to.

Sanofi submitted that the representative then continued to explain the EFFICACY study, its design and primary endpoint of non-inferiority to Lantus, going on to outline the outcomes of the trial and results leading to the conclusion that Levemir did not reach non-inferiority to Lantus, making it clear why she had used the words inferior and non-inferior rather than superior. The representative made it clear that the data was not published in a peer reviewed journal, however it was available at both the Novo Nordisk website and the ClinicalTrials.gov website.

Sanofi stated that there were no further questions around the EFFICACY study or any other studies involving Lantus or Levemir. This then led into a discussion about the use of NPH [neutral protamine Hagedorn], and NICE guidelines. The representative did not tell the group 'there is no reason clinically why you should prescribe Levemir' nor challenge their prescribing. The representative then demonstrated Sanofi's two new blood glucose meters.

Sanofi submitted that the representative did not use any material at the meeting but left a leavepiece relating to the blood glucose meter.

PANEL RULING

The Panel noted that the complainant had alleged that the representative had stated or implied that Levemir had recently failed a non-inferiority trial against Lantus and so there was no reason clinically why Levemir should not be prescribed.

The Panel noted Sanofi's submission that the meeting at issue was organised by the representative in order to discuss the results of the EFFICACY trial, demonstrate Sanofi's new blood glucose meters and provide an update on supply issues for one of Sanofi's products. Sanofi had submitted that although the representative had presented data from the EFFICACY trial she had not used any material to do so.

The Panel noted that according to Novo Nordisk's published clinical trial synopsis, EFFICACY was a randomized, open label, non-inferiority trial. Its primary objective was to compare the efficacy of once daily Levemir vs once daily Lantus, each in combination with metformin, over 26 weeks in type 2 diabetics inadequately controlled on metformin with or without one other oral antidiabetic medicine. Details of the confidence intervals were provided. The authors concluded that after 26 weeks, Levemir could not be claimed non-inferior to Lantus with respect to change in HbA1c. A comparative analysis between treatment arms showed a significant difference in favour of the Lantus arm for the proportion meeting HbA1c targets (both ≤7% and ≤6.5%). No significant differences between treatment arms were found when comparing the same targets but in the absence of hypoglycaemia. The statistical significance of some differences was not clear.

The Panel noted Sanofi's submission that representative briefings made it clear that although the results of the EFFICACY trial were the most recent addition to the Lantus sales message, it formed part of a comprehensive story supporting the place of Lantus in the treatment of type 2 diabetes, and was not a stand-alone result to be delivered in isolation. At the meeting in question, however, it appeared that this was the only study discussed with regard to Lantus and that, contrary to the briefings, it was not delivered as part of an integrated Lantus story.

The Panel noted that a key message in a representatives' briefing document on the EFFICACY study, issued in October 2011 for reactive use only, described it as a 'failed study'. The Panel further noted that a second internal briefing was issued in December 2011 to all field-based promotional teams from the Sanofi brand lead, insulins, entitled 'EFFICACY study Training'. It stated that Sanofi had '…..developed and tested key messages from this study and integrated these in to a strengthened Lantus vs Levemir story which you will get to familiarise yourself with at Cycle 1 meeting'. The brief further stated that in the past week further information had been released regarding EFFICACY which 'really confirms the fact that Lantus is the superior once daily basal insulin, and should be the only choice when a once-daily insulin is needed'.

The Panel noted that a summary of the EFFICACY results presented at Cycle meeting 1 contained the subtitle 'New Ammunition –The Efficacy Study'. The fourth slide entitled 'How excited should we be about Efficacy?' provided a link to a video on YouTube of two wildly excited children opening their Christmas presents. The Panel questioned whether this video provided a balanced impression of the significance of the trial results.

The summary stated whether differences were statistically significant and that no p values were provided in the available data.

Following the trial summary, a slide headed 'Group Practice' instructed the representatives to form in to account teams and take five minutes to familiarise themselves with how the data was represented. Following this, the representatives were to use the remaining 25 minutes in pairs practicing how 'you would verbalise the messages from the Efficacy paper' and to 'Focus on the language you would use, and the type of outcomes you are hoping to achieve with different customer groups'. The Panel was extremely concerned that the representatives had not been given detailed written guidance on how to describe the data from the EFFICACY study.

The final slide of the presentation, entitled 'Lantus Key Message Summary', contained a venn diagram

of three inter-locking circles, each containing one of the statements 'Effective HbA_{1c} Control', 'Simplicity' and 'Reassurance for You and Your Patients'. A speech bubble coming from the 'Simplicity' circle stated 'Lantus is the only true once daily basal insulin'.

The Panel noted that the parties' accounts of what was said at the meeting differed. It was difficult in such circumstances to determine where the truth lay. A decision had to be made on the available evidence. Sanofi submitted that the representative did not tell those present that 'there is no reason clinically why you should prescribe Levemir' nor challenge their prescribing. However, given the statement in the representatives' briefing in relation to Lantus being the only choice when a once daily insulin was required, encouragement at the Cycle meeting 1 of the representatives to use their own words to communicate the results of the EFFICACY 'message' and the impression given to representatives from the YouTube video, the Panel considered that, on the balance of probabilities, the representative had misleadingly implied that there was no clinical reason to prescribe Levemir. A breach of Clause 7.2 was ruled. The implication could not be substantiated and a breach of Clause 7.4 was ruled. The indication for Levemir was, *inter alia*, as part of a basal-bolus insulin regimen once or twice daily depending on patients' needs, and to imply otherwise was disparaging to the medicine. In addition the Panel considered that the implication that there was no clinical reason to prescribe Levemir was also disparaging. A breach of Clause 8.1 was ruled.

The representative in question had not maintained high standards and a breach of Clause 15.2 was ruled. The claim in the representatives' briefing document that Lantus 'should be the only choice when a once-daily basal insulin is needed' advocated a course of action that was likely to be in breach of the Code. In addition the Panel noted its critical comment on each of the representatives' briefing materials above and considered that separately and cumulatively they advocated a course of action likely to be in breach of the Code. A breach of Clause 15.9 was ruled. The Panel considered that by briefing its representatives that Lantus was the only choice when a once daily insulin was required and by failing to provide adequate written guidance to representatives on how to describe the EFFICACY study, Sanofi had not maintained high standards and a breach of Clause 9.1 was ruled.

Complaint received **3 February 2012**

Case completed **17 April 2012**

PHARMACIST/CLINICAL SENIOR LECTURER v GLAXOSMITHKLINE

Promotion of Seretide

A pharmacist and clinical senior lecturer, complained about a Seretide (salmeterol/fluticasone) email sent by GlaxoSmithKline via eGuidelines.co.uk. Seretide was indicated for use in patients with asthma or chronic obstructive pulmonary disease (COPD).

The heading to the email stated that Seretide now delivered even greater value to the NHS and stated that 'The price of Seretide Accuhaler 100 has been reduced by 42% to £18 and is now the same price as the Seretide Evohaler 50'. A bullet point which followed stated 'Seretide is priced competitively compared to other ICS/LABA [inhaled corticosteroids/long-acting beta-agonist] combinations at equivalent doses'. This claim was referenced to MIMS, January 2012. A second bullet point stated 'Prescribed appropriately, Seretide can help achieve NHS quality and productivity targets' and was referenced to Doull *et al* (2007) and Briggs *et al* (2010).

The complainant alleged that the claim that Seretide products were competitively priced compared with other ICS/LABA products due to a 42% decrease in price of the Seretide Accuhaler 100 was incorrect. The email did not show how the cost had been calculated other than a reference to MIMS. The complainant submitted that the cost of a Seretide inhaler was higher than all the competitor products across the whole dose range. Depending on the dose and product chosen, the variation was at least 8% and the claim was, therefore, misleading. The complainant further alleged that the claim that Seretide was priced competitively and could help the NHS quality and productivity targets could not be substantiated.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that, from the information provided by GlaxoSmithKline, at low and medium doses, Seretide Accuhaler and Seretide Evohaler were the same price and neither was the most expensive nor the cheapest ICS/LABA combination available. At high dose, Seretide Accuhaler was the least expensive and Seretide Evohaler the second least expensive.

The Panel considered that the claim at issue, 'Seretide is priced competitively compared to other ICS/LABA combinations at equivalent doses', did not imply that the Seretide preparations were the least expensive combinations but rather that they were somewhere in the middle of the price range. This was the case for low and medium doses of the Seretide preparations, with the high dose preparations being the least expensive, as noted above. The Panel noted that it was clear that the comparison was with equivalent doses. However the dose details were not given in the email. The Panel did not consider that the claim was misleading as alleged and ruled no breach of the Code. The statement was capable of substantiation and no breach of the Code was ruled.

The Panel noted that the claim 'Prescribed appropriately, Seretide can help achieve NHS quality and productivity targets', was referenced to Doull *et al* and Briggs *et al*. The Panel further noted that national guidance described the treatment of asthma as a series of steps dependent on disease severity and response to current treatment. The third step, if symptoms could not be controlled with an ICS alone was to add in a LABA. The Panel noted GlaxoSmithKline's submission that 76% of such patients were eligible for the lowest dose of Seretide (either Seretide Accuhaler 100 or Seretide Evohaler 50), yet only 20% of them received this lowest dose and subsequently a significant proportion of Seretide patients were commenced on doses that were higher than necessary. The Panel considered that it was not unreasonable to assume that reducing the cost of Seretide Accuhaler 100 could lead to cost savings.

The Panel noted that Doull *et al* sought to determine where in the national asthma guidance it was cost-effective to use Seretide in the treatment of chronic asthma in adults and children. The authors concluded that for patients uncontrolled on beclometasone 400mcg per day or equivalent it was cost-effective to switch to Seretide compared with increasing the dose of ICS. Briggs *et al* reported the analysis of economic data from the Towards a Revolution in COPD (TORCH) study which aimed to inform decision makers of the potential cost-effectiveness of alternative treatments for COPD. The authors concluded that Seretide was more effective and had a lower incremental cost-effectiveness ratio (compared with placebo) than either fluticasone or salmeterol alone.

The Panel noted that the cost of one presentation of Seretide had been reduced in price. Further if all presentations of Seretide were prescribed appropriately then this might help achieve NHS quality and productivity targets. The Panel did not consider that the claim 'Prescribed appropriately Seretide can help achieve NHS quality and productivity targets' was misleading as alleged and no breach of the Code was ruled. The claim was capable of substantiation and no breach of the Code was ruled.

A pharmacist and clinical senior lecturer complained about an email sent by GlaxoSmithKline UK Limited via eGuidelines.co.uk headed 'Seretide (salmeterol xinafoate/fluticasone propionate) now delivers even

greater value to the NHS'. Seretide was indicated for use in patients with asthma or chronic obstructive pulmonary disease (COPD).

The email, which was signed by a marketing director respiratory and allergy stated that 'The price of Seretide Accuhaler 100 has been reduced by 42% to £18 and is now the same price as the Seretide Evohaler 50'. A bullet point which followed stated 'Seretide is priced competitively compared to other ICS/LABA [inhaled corticosteroids/long-acting beta-agonist] combinations at equivalent doses'. This claim was referenced to MIMS, January 2012. A second bullet point stated 'Prescribed appropriately, Seretide can help achieve NHS quality and productivity targets' and was referenced to Doull *et al* (2007) and Briggs *et al* (2010). The email had been sent to GPs, pharmacists, medicines management professionals and healthcare managers.

COMPLAINT

The complainant alleged that the claim that Seretide products were competitively priced compared with other ICS/LABA products due to a 42% decrease in price of the Seretide Accuhaler 100 was incorrect. The email did not show how the cost had been calculated other than a reference to MIMS. The complainant submitted that the cost of a Seretide inhaler was higher than all the competitor products across the whole dose range. Depending on the dose and product chosen, the variation was at least 8% and the claim was, therefore, misleading. The complainant further alleged that the claim in the circular that Seretide was priced competitively and could help the NHS quality and productivity targets could not be substantiated.

The complainant stated that his main concern was the lack of transparency in the health economic calculations and the deductions implied there from. The complainant considered that an explanation as to how the claims made could be achieved would have been helpful.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

GlaxoSmithKline submitted that the email informed recipients that the price of the Seretide Accuhaler 100 had been reduced by 42%, from £31.19 to £18, on 1 January 2012. The equivalently dosed Seretide Evohaler 50 also cost £18 and so the Accuhaler and the Evohaler in this dose category were now the same price.

This cost reduction was a simple calculation and GlaxoSmithKline considered that it was presented in a clear, fair and balanced manner and was not therefore in breach of Clauses 7.2 or 7.4 of the Code.

With regard to the claim 'Seretide is priced competitively compared to other ICS/LABA combinations at equivalent doses', GlaxoSmithKline submitted that not all inhaled corticosteroids were the same and had different potencies. The British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) Guideline on the Management of Asthma recommended equivalent doses of inhaled corticosteroids and compared them with another inhaled corticosteroid, beclometasone (BDP).

The corticosteroid in Seretide was fluticasone propionate which had a different potency from BDP or budesonide (the inhaled corticosteroid contained in AstraZeneca's product Symbicort). The BDP in Chiesi's product Fostair was characterised by an extra fine particle size distribution which resulted in a more potent effect than standard formulations of BDP.

The BTS/SIGN Guideline stated that 'fluticasone provides equal clinical activity to both BDP and budesonide at half the dose' and that 200mcg of BDP in Fostair was equivalent to 400mcg of standard BDP. Therefore, when comparing different inhaled corticosteroids, a Seretide 200mcg inhaler would be comparable to a 400mcg inhaler of either BDP or budesonide (the inhaled corticosteroid contained in Symbicort) or a 200mcg inhaler of Fostair.

GlaxoSmithKline provided a table setting out the various different ICS/LABA combination inhalers currently available, their dose-equivalence (at low, mid and high doses as defined by the Global Initiative for Asthma) and the 30 day cost.

	Seretide Accuhaler (salmeterol/ fluticasone)	Seretide Evohaler (salmeterol/ fluticasone)	Fostair (formoterol/ beclometasone)	Symbicort (formoterol/ budesonide)
Low Dose ICS (200 - 500 mcg BDP)	£18.00	£18.00	£14.66	£19.00 (200/6 1 puff bd) or £33.00 (100/6 2 puffs bd)
Mid Dose ICS (>500 - 1000 mcg BDP)	£35.00	£35.00	£29.32	£38.00 (200/6 2 puffs bd)
High Dose ICS (>1000 - 2000 mcg BDP)	£40.92	£59.48	Not licensed	£76.00 (400/12 2 puffs bd)

GlaxoSmithKline submitted that the table showed that, at equivalent doses, Seretide was not the most expensive combination therapy across the product range. At low and mid doses, Seretide was neither the most expensive nor the cheapest ICS/LABA combination and furthermore, for patients requiring a high-dose inhaled corticosteroid, Seretide Accuhaler 500 was the cheapest ICS/LABA combination available.

GlaxoSmithKline submitted that MIMS was recognised as an accepted source for providing the most up-to-date and accurate prices of medicines available through the NHS. In addition to specifying the prices of the individual inhalers, MIMS also provided clear and accurate information on the doses per unit and in the guidelines section the BDP dose equivalence of the different ICS/LABA combinations currently available. GlaxoSmithKline believed, therefore, that MIMS was an appropriate reference to support the claim that 'Seretide is competitively priced compared to other ICS/LABA combinations at equivalent doses', which was fair, balanced and capable of substantiation. GlaxoSmithKline denied breaches of Clauses 7.2 and 7.4.

GlaxoSmithKline noted that the Quality, Innovation, Productivity and Prevention (QIPP) agenda, a strategy introduced in 2009 by the Department of Health, aimed to improve the quality and delivery of NHS care and reduce costs to make £20billion efficiency savings by 2014/15. The actual strategies adopted by local health providers depended on individual strategic health authorities and primary care trusts. The work-streams aligned to quality aimed to provide high quality care and those aligned to productivity aimed to drive efficiency savings.

GlaxoSmithKline stated that asthma treatment should be titrated to the severity of disease. The BTS/SIGN Guideline recommended a step-wise approach to management and stated that in adults who required regular preventer therapy (step 2) 400mcgs of BDP was an appropriate starting dose. If a patient was inadequately treated on an inhaled corticosteroid alone, then the guidelines recommended adding in a LABA (step 3) before increasing the dose of the steroid (ie move from a low dose steroid 400mcg to a mid-dose steroid 800mcg). The BTS/SIGN Guideline stated that:

> 'A stepwise approach aims to abolish symptoms as soon as possible and to optimise peak flow by starting treatment at the level most likely to achieve this. Patients should start treatment at the step most appropriate to the initial severity of their asthma'.

GlaxoSmithKline submitted that of patients currently taking an inhaled corticosteroid alone (step 2), in whom the next recommended step would be Seretide or an equivalent ICS/LABA (step 3), 76% were eligible for the lowest dose Seretide preparations according to their current dose of steroid. However, at present, only 20% of adults with asthma moving from inhaled corticosteroid alone to Seretide were appropriately prescribed Seretide at the lowest dose (ie the Seretide Accuhaler 100 or the Seretide Evohaler 50).

GlaxoSmithKline stated that therefore, a significant proportion of new Seretide patients were commenced on doses of inhaled steroid that were higher than necessary. This was clearly not consistent with the BTS/SIGN Guideline and meant that some patients might be over-treated or at higher risk of side-effects. In addition, as the cost of Seretide increased with the dose of steroid, the prescription of doses of Seretide that were higher than necessary had cost implications.

Before January 2012, the Seretide Accuhaler 100 was £31.19 which was more than the equivalently dosed Seretide Evohaler 50 which cost £18 and was also similar in price to the mid-dose Seretide options which both cost £35. By reducing the price of the Seretide Accuhaler 100 to £18, GlaxoSmithKline considered that health professionals might be encouraged, where appropriate, to initiate asthma patients on the lowest dose of Seretide.

The appropriate prescribing of Seretide in asthma might therefore allow health providers to increase adherence with the BTS/SIGN Guideline by starting appropriate patients on the low dose (improving the quality of treatment). This would also reduce prescribing costs (thereby increasing productivity).

GlaxoSmithKline submitted that in the peer-reviewed studies referenced in the email, Seretide was shown to be a cost-effective treatment vs increasing the dose of fluticasone propionate (inhaled steroid alone) in asthma and vs the long-acting beta-agonist salmeterol in COPD.

An asthma example of a QIPP case study on the QIPP website was 'Primary care asthma management to reduce costs and improve outcomes' which focused on improving care for respiratory patients, implementing effective guideline driven prescribing and increased use of combination inhalers where appropriate whilst reducing admissions, referrals and respiratory prescribing costs.

The cost effectiveness study by Doull *et al* in asthma was driven by a systematic review and meta-analysis of 14 large randomised, control trials. It modelled resource utilisation by extrapolating the degree of symptoms to the likelihood of the utilisation of healthcare resource (such as GP visits or hospital admissions). Doull *et al* demonstrated that Seretide could reduce healthcare resource in a cost-effective manner compared with increasing the dose of inhaled steroid alone, which might help the NHS to achieve QIPP quality and productivity targets.

In addition, the National Institute for Health and Clinical Excellence (NICE) performed a technology assessment in 2008 for inhaled corticosteroids in the treatment of chronic asthma in adults and children aged 12 years and over. In Section 4.3.10, NICE stated that 'The Committee considered that treatment with an inhaled corticosteroid plus a long-acting beta-agonist in a single combination device was at least as effective as using the same ingredients in separate devices'. In Section 4.3.11, NICE stated further that 'The Committee also considered that, in people for whom inhaled corticosteroid plus long-acting beta-agonist treatment is appropriate, the least costly delivery method should be used, which is currently a combination device'.

In summary, GlaxoSmithKline believed that the appropriate prescription of Seretide, such as initiating

appropriate patients with asthma on the Seretide Accuhaler 100, and the evidence that Seretide was cost-effective when appropriately prescribed could substantiate the claim, 'Prescribed appropriately, Seretide can help achieve NHS quality and productivity targets'.

GlaxoSmithKline considered that the claim was fair, balanced and could be substantiated; it denied breaches of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that a table in the BTS/SIGN Guideline indicated that 400mcg of BDP was equivalent to 200mcg of Fostair, 200mcg of Seretide and 400mcg of Symbicort. These dose equivalencies were also summarized in a table in MIMS. Both publications also stated that 'These dosage equivalents are approximate and will depend on other factors such as inhaler technique'. The Panel further noted that the Global Initiative for Asthma publication 'Global Strategy for Asthma Management and Prevention' defined a low daily dose of BDP as 200-500mcg, medium daily dose as >500-1000mcg and a high daily dose as >1000-2000mcg.

The Panel noted that the Seretide Accuhaler was available in three strengths; 100mcg, 250mcg and 500mcg, all of which were to be administered as one inhalation twice a day. Fostair was available as a 100mcg preparation (to be administered as one or two inhalations twice daily) and Symbicort as 100mcg and 200mcg preparations (to be administered as one or two inhalations twice daily) and a 400mcg preparation (to be administered as one inhalation twice daily).

Given the dose definitions above and the information submitted by GlaxoSmithKline, the Panel noted that the 30 day cost of treatment at equivalent doses with low dose ICS/LABA combination was £18 for Seretide Accuhaler, £18 for Seretide Evohaler, £14.66 for Fostair and either £19 or £33 for Symbicort (depending on whether the 100mcg or 200mcg preparation was used). The 30 day treatment cost at equivalent doses for medium dose ICS/LABA was £35 for Seretide Accuhaler, £35 for Seretide Evohaler, £29.32 for Fostair and £38 for Symbicort. The 30 day treatment cost at equivalent doses for high doses of these medicines was £40.92 for Seretide Accuhaler, £59.48 for Seretide Evohaler and £76 for Symbicort. Fostair was not licensed above 400mcg daily (the dose equivalent of 800mcg BDP).

The Panel noted that at low and medium doses, both Seretide preparations were the same price and neither was the most expensive nor the cheapest ICS/LABA combination available. At high dose, Seretide Accuhaler was the least expensive and Seretide Evohaler the second least expensive.

The Panel considered that the claim at issue, 'Seretide is priced competitively compared to other ICS/LABA combinations at equivalent doses', did not imply that the Seretide preparations were the least expensive combinations but rather that they were somewhere in the middle of the price range. This was the case for low and medium doses of the Seretide preparations, with the high dose preparations being the least expensive, as noted above. The Panel noted that it was clear that the comparison was with equivalent doses. However the dose details were not given in the email. The Panel did not consider that the claim was misleading as alleged and ruled no breach of Clause 7.2. The statement was capable of substantiation and no breach of Clause 7.4 was ruled.

In relation to the claim 'Prescribed appropriately, Seretide can help achieve NHS quality and productivity targets', the Panel noted that the aim of the Department of Health's QIPP agenda was to improve the quality of care delivered by the NHS whilst making up to £20billion of efficiency savings by 2014-15. The Panel noted that the references given for the claim at issue were Doull *et al* and Briggs *et al*. The Panel further noted that the BTS/SIGN Guideline described the treatment of asthma as a series of steps dependent on disease severity and response to current treatment. The third step, if symptoms could not be controlled with an ICS alone was to add in a LABA. The Panel noted GlaxoSmithKline's submission that 76% of such patients were eligible for the lowest dose of Seretide (either Seretide Accuhaler 100 or Seretide Evohaler 50), yet only 20% of them received this lowest dose and subsequently a significant proportion of Seretide patients were commenced on doses that were higher than necessary. The Panel considered that it was not unreasonable to assume that reducing the cost of Seretide Accuhaler 100 could lead to cost savings.

It was difficult to see that lowering the cost of Seretide Accuhaler 100 would necessarily encourage health professionals to use lower doses as submitted by GlaxoSmithKline. There was nothing in the email to encourage health professionals to consider this point.

The Panel noted that Doull *et al* sought to determine where in the BTS/SIGN asthma guidance it was cost-effective to use Seretide in the treatment of chronic asthma in adults and children. The authors concluded that for patients uncontrolled on BDP 400mcg per day or equivalent it was cost-effective to switch to Seretide compared with increasing the dose of ICS. Briggs *et al* reported the analysis of economic data from the Towards a Revolution in COPD (TORCH) study which aimed to inform decision makers of the potential cost-effectiveness of alternative treatments for COPD. The authors concluded that Seretide was more effective and had a lower incremental cost-effectiveness ratio (compared with placebo) than either fluticasone or salmeterol alone.

The Panel noted that the cost of one presentation of Seretide had been reduced in price. Further if all presentations of Seretide were prescribed appropriately then this might help achieve NHS quality and productivity targets. The Panel did not consider that the claim 'Prescribed appropriately Seretide can help achieve NHS quality and productivity targets' was misleading as alleged and no breach of Clause 7.2 was ruled. The claim was capable of substantiation and no breach of Clause 7.4 was ruled.

Complaint received **7 February 2012**

Case completed **18 April 2012**

CASE AUTH/2483/2/12

CONSULTANT IN SEXUAL HEALTH v PFIZER

Promotion of Prevenar 13

A consultant in sexual health and HIV medicine, complained about a Prevenar 13 (pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) leavepiece issued by Pfizer. Prevenar 13 was indicated, *inter alia*, for active immunisation for the prevention of invasive disease caused by *Streptococcus pneumoniae* in adults aged 50 years and older.

The one page leavepiece at issue was printed on both sides. One side was headed with the Prevenar 13 product logo in the top left hand corner. A white box of text, diagonally opposite the product logo, stood out prominently from the navy blue background and stated in large, navy blue capital letters 'HIV [human immunodeficiency virus] and invasive pneumococcal disease'. Below the boxed text, in smaller bright yellow type, was the statement 'New Indication' and then below this in white type against the navy blue background was the heading 'Adult indication' followed by, in much smaller white type, 'Prevenar 13 is indicated for active immunisation for the prevention of invasive pneumococcal disease caused by *Streptococcus pneumoniae* in adults aged 50 years and older'.

The complainant alleged that the leavepiece implied that Prevenar 13 was newly indicated in HIV infection which was not so and in the very small print prescribing information there were warnings about the lack of safety data for HIV infection. The indication referred to beneath the large banner about HIV was in fact regarding patients aged over 50 years of age.

The detailed response from Pfizer is given below.

The Panel noted that the Prevenar 13 Summary of product characteristics (SPC) stated that individuals with impaired immune responsiveness due to, *inter alia*, HIV infection might have a reduced antibody response to active immunisation and that safety and immunogenicity data for Prevenar 13 were not available for such patients and that vaccination should be considered on an individual basis. There was no reference in the leavepiece to this caution other than in the prescribing information.

The Panel considered that the leavepiece implied that use in HIV and invasive pneumococcal disease was a new indication for Prevenar 13. This was of particular concern given the statements in the SPC.

The Panel considered that the leavepiece did not promote Prevenar 13 in accordance with the terms of its marketing authorization, was inconsistent with the particulars in its SPC and misleading with regard to the licensed indication. High standards had not been maintained. Three breaches of the Code were ruled. The Panel noted that Pfizer had acknowledged all of these breaches and had already withdrawn the leavepiece.

The Panel considered that the legibility of the prescribing information was not unacceptable noting in particular the advice on legibility set out in the Code. The Panel ruled no breach of the Code.

A consultant in sexual health and HIV medicine complained about a Prevenar 13 (pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) leavepiece (ref VAC291) issued by Pfizer. Prevenar 13 was indicated, *inter alia*, for active immunisation for the prevention of invasive disease caused by *Streptococcus pneumoniae* in adults aged 50 years and older.

The material at issue was a one page leavepiece printed on both sides. One side was headed with the Prevenar 13 product logo in the top left hand corner. A white box of text, which was diagonally opposite the product logo, stood out prominently from the navy blue background and stated in large, navy blue capital letters 'HIV [human immunodeficiency virus] and invasive pneumococcal disease'. Below the boxed text, in smaller bright yellow type, was the statement 'New Indication' and then below this in white type against the navy blue background was the heading 'Adult indication' followed by, in much smaller white type, 'Prevenar 13 is indicated for active immunisation for the prevention of invasive pneumococcal disease caused by *Streptococcus pneumoniae* in adults aged 50 years and older'. The prescribing information appeared in black type on a white background on the lower half of the page.

The reverse side of the leavepiece referred to the increased risk of invasive pneumococcal infection in adults with HIV and the efficacy of pneumococcal conjugate vaccines in preventing such infections in that population. At the bottom of the page was the heading 'Prevenar 13 New Indication' below which was stated 'Prevenar 13 is now indicated for active immunisation for the prevention of invasive disease caused by *Streptococcus pneumoniae* in adults aged 50 years and older'.

COMPLAINT

The complainant alleged that the leavepiece implied that there was a new indication for Prevenar 13 in HIV infection, whereas in fact it was not so authorized and in the very small print prescribing information there were warnings about the lack of safety data for HIV infection. The indication referred to beneath the large banner about HIV was in fact regarding patients aged over 50 years of age.

The complainant further submitted that on the reverse side of the leavepiece the HIV theme continued, although studies cited related to previous versions of the vaccine and again appeared to imply that this particular PCV-13 (pneumococcal conjugate vaccine 13) vaccine might reduce invasive pneumococcal disease and this use was licensed in the UK.

The complainant accepted that there might be theoretical benefits to using pneumococcal conjugate vaccines but he objected to marketing spin that implied that Prevenar 13 was safe, effective and had a marketing authorization for use in HIV infection and the matter was concluded. The HPA (Health Protection Agency) had complicated matters by recommending introduction of Prevenar 13 in a report on HIV infection in advance of formally considering this as part of the Green Book update later in 2012, so the complainant accepted that the situation was blurred. However, he considered that Pfizer had strayed over the boundary with its leavepiece.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 3.2, 4.1, 7.2 and 9.1 of the Code.

RESPONSE

Pfizer submitted that whilst it had intended to raise awareness of an important treatment option for a vulnerable patient group, it recognised that the leavepiece had not adhered to the Code. The leavepiece was used from 19 January by representatives with health practitioners in HIV, sexual medicine and genitourinary medicine.

In consideration of Clause 3.2, Pfizer submitted that it had taken account of the two different elements which together made up the clause; firstly the promotion of a medicine must be in accordance with the terms of its marketing authorization and secondly must not be inconsistent with the particulars listed in its summary of product characteristics (SPC).

Pfizer submitted that Prevenar 13 was indicated in adults aged 50 years and over; some of these patients would have HIV and were at increased risk of pneumococcal disease. The licence for Prevenar 13 did not exclude use of the medicine in this group. The European Public Assessment Report (EPAR) for Prevenar 13 noted that 'clinical studies in human immunodeficiency virus (HIV)-infected adult populations have provided evidence that conjugated vaccines exhibit noted efficacy against invasive pneumococcal disease and possibly pneumonia, in circumstances where [the current standard of care pneumococcal vaccine] has not afforded such protection to these immune-compromised adults'. Pfizer therefore did not consider that it had breached the first element of Clause 3.2 (as set out above). However, Pfizer stated that it recognised that the leavepiece did not draw attention to the following wording in the Prevenar 13 SPC:

> 'Individuals with impaired immune responsiveness, whether due to the use of immuno-suppressive therapy, a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced antibody response to active immunization.
>
> Safety and immunogenicity data for Prevenar 13 are not available for individuals in specific immuno-compromised groups (e.g., congenital or acquired splenic dysfunction, HIV infected, malignancy, haematopoietic stem cell transplant, nephrotic syndrome) and vaccination should be considered on an individual basis.'

Pfizer submitted that this therefore made the leavepiece inconsistent with the SPC and breached the second element of Clause 3.2. As Clause 3.2 was made up of two elements and it agreed that the leavepiece did not meet the requirements of the second element, Pfizer acknowledged a breach of Clause 3.2.

Pfizer considered that the prescribing information that was an integral part of the leavepiece was in line with the requirements of the Code, but the company could understand that the quality of the scanned copy provided by the complainant made this difficult to ascertain. Pfizer submitted that the original piece did not breach Clause 4.1.

Pfizer stated that as the current material might be misinterpreted to suggest a specific indication in HIV regardless of age, and with evidence from the complainant of the confusion this might cause, it acknowledged a breach of Clause 7.2.

In view of the acknowledged breaches of Clauses 3.2 and 7.2, Pfizer considered it had not maintained high standards and acknowledged a breach of Clause 9.1.

Pfizer submitted that it took this matter extremely seriously and confirmed that it had already withdrawn the leavepiece and briefed its sales team accordingly.

PANEL RULING

The Panel noted the statement in Section 4.4, Special Warnings and Precautions for Use, of the Prevenar 13 SPC that individuals with impaired immune responsiveness whether due to a number of factors including HIV infection or other causes might have a reduced antibody response to active immunisation and that safety and immunogenicity data for Prevenar 13 were not available for individuals in specific immuno-compromised groups, including those with HIV and that vaccination should be considered on an individual basis. There was no reference in the leavepiece to this caution other than in the prescribing information.

The Panel examined the leavepiece and considered that overall it gave the impression that use in HIV and invasive pneumococcal disease was a new indication for Prevenar 13. This was of particular concern given the statements in the SPC.

The Panel considered that the leavepiece did not promote Prevenar 13 in accordance with the terms of

its marketing authorization and was inconsistent with the particulars in its SPC. A breach of Clause 3.2 was ruled. The Panel considered that the leavepiece was misleading with regard to the licensed indication of Prevenar 13 and ruled a breach of Clause 7.2. The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted that Pfizer had acknowledged all of these breaches of the Code and had already withdrawn the leavepiece.

The Panel noted that in the copy of the leavepiece submitted by the complainant, the prescribing information was very difficult to read. The complainant had referred to 'very small print'. However, the Panel considered that the legibility of the prescribing information in the original leavepiece provided by Pfizer was not unacceptable noting in particular the advice on legibility set out in the supplementary information to Clause 4.1. The Panel ruled no breach of Clause 4.1.

Complaint received **28 February 2012**

Case completed **17 April 2012**

THERAPIST v SANOFI

Provision of information

A clinical hypnotherapist/psychoanalyst/behavioural therapist alleged that Sanofi had been obstructive in that it had refused to provide information about Clexane (enoxaparin) when he had telephoned the company. Clexane was marketed for, *inter alia*, the prophylaxis of thromboembolic disorders of venous origin, in particular those which might be associated with orthopaedic or general surgery, and the prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness.

The complainant, who had previously suffered thromboembolic events, had wanted to know the best time to inject himself with Clexane prior to a nine hour flight. Although the complainant understood that Sanofi had 'lots of data' regarding pre-flight use, it would not pass any on to him; the company asked him to ask his doctor to call but this was somewhat difficult.

The detailed response from Sanofi is given below.

The Panel noted that the complainant had called Sanofi's medical information department in relation to his possible personal use of Clexane prior to a nine hour flight. The complainant had wanted to know how long beforehand he should inject the medicine. There was no relevant information in the SPC and it appeared that Clexane was not indicated for the prevention of venous thromboembolic events in such circumstances. The Panel noted that the complainant did not appear to be a health professional.

The Panel noted Sanofi's submission that the medical information officer concerned had informed the complainant that whilst there was data on the use of Clexane prior to long journeys, the company could not comment on his personal medical situation and he would need to ask his own doctor or pharmacist for advice on what dosing regimen to use. The Panel further noted Sanofi's submission that the medical information officer also stated that if the complainant's doctor or pharmacist required more information Sanofi would be happy to supply it to them if they contacted the company.

Given that the enquiry related to a personal medical matter, the Panel considered that Sanofi had complied with the requirements of the Code; no information was supplied to the complainant with regard to Clexane's use in venous thromboembolism. The Panel ruled no breaches of the Code.

A clinical hypnotherapist/psychoanalyst/behavioural therapist complained about the lack of information he had been given when he had telephoned Sanofi about the use of Clexane (enoxaparin) prior to a long journey.

Clexane was marketed for, *inter alia*, the prophylaxis of thromboembolic disorders of venous origin, in particular those which might be associated with orthopaedic or general surgery, and the prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness.

COMPLAINT

The complainant stated that he telephoned Sanofi to find out the best time to inject Clexane prior to a nine hour flight. The complainant submitted that he was told that Sanofi had 'lots of data' regarding pre-flight use, however Sanofi had stated that it would not pass this information to him. The complainant stated that his GP and pharmacist had no idea what time parameter to use this medicine. Sanofi told the complainant that he would have to get his doctor to call, which was somewhat difficult.

The complainant submitted that on the Sanofi website there was an abundance of clinical information regarding Clexane, mainly pre- and post-operative care.

The complainant submitted that as he had suffered previous DVTs [deep vein thrombus] and pulmonary embolism, it would be pertinent (considering he was injecting himself) to understand recent relevant data on this subject. He also considered this information should be included for many hundreds of people who had been prescribed this medicine. There seemed to be an obstructive element in providing important information.

When writing to Sanofi, the Authority asked it to respond in relation to Clauses 22.2, 22.3 and 9.1 of the Code.

RESPONSE

Sanofi confirmed that the complainant had telephoned its medical information department about his treatment with Clexane; he wanted to know the correct time to administer the injection in relation to flights and long car journeys.

Sanofi submitted that whilst Clexane was licensed for the prophylaxis of thromboembolic disorders of venous origin, in particular those associated with orthopaedic or general surgery, the summary of product characteristics (SPC) did not give a specific dosing regimen for the prevention of in-flight thrombosis. The complainant was thus informed that whilst Sanofi knew of data detailing the use of Clexane in this particular indication, it was unable to comment on his personal medical situation and he would need to ask his own doctor or pharmacist for advice on what dosing regimen to use. Sanofi submitted that the medical information officer stated

that if the complainant's doctor or pharmacist required more information, Sanofi would be happy to supply it to them in response to a direct request.

Sanofi submitted that it was unable to comment on the complainant's assertion that its website contained 'an abundance of clinical information regarding Clexane' as the only UK specific website (www.sanofi.co.uk) did not contain any clinical data regarding Clexane but did include the SPC.

Sanofi stated that as the complainant asked for advice on a personal medical matter, it considered that its medical information officer had acted appropriately.

In summary, Sanofi denied any breach of the Code. Clause 22.3 was clearly adhered to as the patient was referred back to his own health professional for advice. Sanofi could not see the relevance of Clause 22.2 as no information was provided directly to the patient and Sanofi did not make any information available indirectly. Sanofi submitted that high standards had been maintained and therefore there was no breach of Clause 9.1.

PANEL RULING

The Panel noted that the complainant had called Sanofi's medical information department in relation to his possible personal use of Clexane prior to a nine hour flight. The complainant had wanted to know how long beforehand he should inject the medicine. There was no relevant information in the SPC and it appeared that Clexane was not indicated for the prevention of venous thromboembolic events in such circumstances.

The Panel noted that the complainant was a clinical hypnotherapist/psychoanalyst/behavioural therapist. On the information provided by the complainant he did not appear to be a health professional. The term 'health professional' in the Code included members of the medical, dental, pharmacy and nursing professions and any other person who in the course of their professional activities might prescribe, supply or administer a medicine.

Clause 23.2 required that requests from individual members of the public on personal medical matters be refused and the enquirer recommended to consult his or her own doctor, other prescriber or other health professional. The Panel noted Sanofi's submission that the medical information officer concerned had informed the complainant that whilst Sanofi was aware of data on the use of Clexane prior to long journeys, it was unable to comment on his personal medical situation and he would need to ask his own doctor or pharmacist for advice on what dosing regimen he should use. The Panel further noted Sanofi's submission that the medical information officer also stated that if the complainant's doctor or pharmacist required more information Sanofi would be happy to supply it to them if they contacted the company.

Given that the enquiry related to a personal medical matter, the Panel considered that Sanofi had complied with the requirements of Clause 22.3 and ruled no breach of that clause. As no information was supplied to the complainant with regard to Clexane's use in venous thromboembolism, the Panel ruled no breach of Clause 22.2. The Panel noted its rulings above and consequently ruled no breach of Clause 9.1.

Complaint received **29 February 2012**

Case completed **11 April 2012**

CODE OF PRACTICE REVIEW – May 2012

Cases in which a breach of the Code was ruled are indexed in **bold type.**

2327/6/10	**MHRA v Grünenthal**	**Promotion of tapentadol**	**Breaches Clauses 2, 3.1 and 9.1** **Audit required by Appeal Board** **Three further Audits required by Appeal Board** **Public reprimand required by Appeal Board**	**No appeal** **Report from Panel to Appeal Board**	**Page 3**
2442/10/11	**Pharmacosmos/ Director v Vifor**	**Breach of undertaking**	**Breaches Clauses 2 and 9.1** **Two breaches Clause 25**	**No appeal**	**Page 13**
2444/10/11	**General Practitioner v Boehringer Ingelheim**	**Pradaxa website**	**Breach Clause 4.6**	**Appeal by complainant**	**Page 17**
2448/10/11	Pharmacist v Boehringer Ingelheim	Promotion of Pradaxa	No breach	Appeal by respondent	Page 23
2449/11/11 and 2450/11/11	General Practitioner v Boehringer Ingelheim and Lilly	Promotion of Trajenta	No breach	Appeal by complainant	Page 32
2451/11/11	**Merck Serono v Sandoz**	**Omnitrope patient support items**	**Two breaches Clause 18.2**	**No appeal**	**Page 40**
2452/11/11	Pharmacist v Pierre Fabre	Conduct of representative	No breach	No appeal	Page 44
2456/11/11	General Practitioner v Boehringer Ingelheim	e-Promotion of Pradaxa	No breach	No appeal	Page 48
2461/12/11	Anonymous v AstraZeneca	Conduct of representative	No breach	No appeal	Page 51
2462/12/11	Meda v ALK-Abelló	Jext website	No breach	No appeal	Page 54
2464/12/11	Healthcare Journalist v Novartis	Galvus press release	No breach	No appeal	Page 57
2465/12/11	**PCT Prescribing support pharmacist v Astellas**	**Qutenza journal insert**	**Two breaches Clause 7.2**	**No appeal**	**Page 61**
2467/12/11 and 2468/12/11	**Anonymous v Boehringer Ingelheim and Pfizer**	**Promotion of Spiriva**	**Breach Clauses 7.11 and 18.2**	**No appeal**	**Page 64**

2469/12/11	**Voluntary admission by Bayer**	**Symposium invitation**	**Breaches Clauses 3.2, 4.1, 4.3, 4.10, 9.1, 9.8 and 14.1** **Two breaches Clause 22.1**	**No appeal**	**Page 66**
2470/1/12	**Anonymous v Novo Nordisk**	**Arrangements for a meeting**	**Breaches Clauses 15.2 and 19.1**	**Appeal by respondent**	**Page 69**
2471/1/12	**Anonymous v Sanofi**	**Arrangements for a meeting**	**Breaches Clauses 15.2 and 19.1**	**Appeal by respondent**	**Page 74**
2472/1/12	**Shire v Flynn**	**Medikinet leavepiece**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 78**
2373/1/12	**Voluntary admission by Vifor**	**Ferinject advertisement**	**Three breaches Clause 14.1**	**No appeal**	**Page 82**
2476/2/12	Anonymous v Allergan	Conduct of employees	No breach	No appeal	Page 84
2477/2/12	**Consultant physician v Sanofi**	**Conduct of representative**	**Breaches Clauses 7.2, 7.4, 8.1, 9.1, 15.2 and 15.9**	**No appeal**	**Page 86**
2478/2/12	Pharmacist/Clinical senior lecturer v GlaxoSmithKline	Promotion of Seretide	No breach	No appeal	Page 92
2483/2/12	**Consultant in sexual health v Pfizer**	**Promotion of Prevenar 13**	**Breaches Clauses 3.2, 7.2 and 9.1**	**No appeal**	**Page 96**
2484/2/12	Therapist v Sanofi	Provision of information	No breach	No appeal	Page 99

PMCPA | Prescription Medicines Code of Practice Authority

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself. Compliance with the Code is obligatory for ABPI member companies and, in addition, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of Internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member is neither present nor participates 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 Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, are always in a majority when matters are considered by the Appeal Board.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.