NUMBER 72 MAY 2011

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.

CODE AWARENESS WEEK - 2011

Code Awareness Week took place on 4-8 April. A number of companies participated and various publications about the Code were distributed.

The new e-learning module on the Code for health professionals was launched at 12 Whitehall on 4 April, Cardiff on 7 April and Edinburgh on 8 April. The presentations were well received and prompted a range of questions from the audiences. The module is available on the PMCPA website.

PUBLIC REPRIMAND FOR BAYER

Bayer Schering Pharma has been publicly reprimanded by the Code of Practice Appeal Board for providing incomplete information about the distribution of a prescribing policy document for Levitra (vardenafil) (Case AUTH/2333/7/10).

Bayer was involved in the generation and distribution of the prescribing policy document that was described as being 'Supported by an educational grant'. The Appeal Board considered that Bayer's failure to recognise that the document was in fact wholly unacceptable promotional material was a shocking error of judgement and that the overall arrangements and content of the material demonstrated a fundamental lack of understanding of the requirements of the Code. The Appeal Board required an audit of Bayer's procedures in relation to the Code and that Bayer should write to each recipient of the document to ask, where practicable, for its return.

Upon receipt of the audit report the Appeal Board was extremely concerned to learn that the material at issue had been more widely distributed than previously indicated by Bayer. It was vital that responses to the Authority were accurate and gave complete information; the failure to provide comprehensive information was unacceptable.

The Appeal Board required a subsequent re-audit of Bayer's procedures.

Full details of Case AUTH/2333/7/10 can be found at page 3 of this issue of this Review.

HOSPITALITY COSTS AND PROVISION OF ALCOHOL

A company must have a standard operating procedure (SOP), or similar, that sets out its policies on meetings and hospitality and provides a guide as to acceptable costs with regard to meals/refreshments. Clause 19.1 of the Code requires that the costs of subsistence must not exceed that level which the recipients would normally adopt when paying for themselves. Those responsible for relevant SOPs would be well advised to ensure that if only one figure is quoted, then readers are quite clear that this is the *maximum* acceptable cost and not the expected cost.

With regard to the provision of alcohol with a meal, the relevant SOP should be explicit as to the company's position on quantity and type. It is most unlikely that providing alcohol at lunch would be acceptable under the Code. With regard to the type of beverage provided, the Authority would suggest that it is rarely appropriate to provide sparkling wines or liqueurs.

WE ARE MOVING ...

The PMCPA is moving offices from 12 Whitehall to 7th Floor, Southside, 105 Victoria Street, London SW1E 6QT. The change of address will be effective by Tuesday, 31 May. All correspondence should be directed accordingly. All other lines of communication including, telephone, email and fax remain unchanged.

NEW DEPUTY SECRETARY APPOINTED

The changes to the Constitution and Procedure mean that from 1 January 2011 the Authority consists of the Director, Deputy Director, Secretary and Deputy Secretary. Etta Logan was appointed by the ABPI Board of Management as the Deputy Director and Jane Landles as the Secretary. The ABPI Board of Management has now appointed Ros Henley to be the new Deputy Secretary to the Authority. Ros has a biology degree and a legal qualification. She has extensive industry experience, including as a nominated signatory, with Takeda. Ros joins the Authority in June. We congratulate Ros on her appointment. We are looking forward to working with her and to her contribution to the work of the Authority.

CODE OF PRACTICE TRAINING

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

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

The next Code of Practice seminar date on which places remain available is:
Tuesday, 12 July 2011

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

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

HOW TO CONTACT THE AUTHORITY

Our address is:
Prescription Medicines Code of Practice Authority
12 Whitehall, London SW1A 2DY

www.pmcpa.org.uk

Telephone:	020 7747 8880
Facsimile:	020 7747 8881

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or email lmatthews@pmcpa.org.uk).

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

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

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

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

ENGLISH ENGLISH AND AMERICAN ENGLISH

Words such as 'authorized' are spelt in the Code of Practice for the Pharmaceutical Industry with a 'z' rather than an 's'. Occasionally comment is made that an 's' should be used because using a 'z' in such words is American English. The PMCPA disputes that that is so. The use of 'z' is well established in English English.

The Shorter Oxford English Dictionary, which the PMCPA regards as an authoritative source, uses 'z' as the prime spelling, giving 's' only as a variant.

The guide to the use of the dictionary states:

'This dictionary follows the tradition of Oxford University Press in using –ize (and corresponding –ization, -izer, etc.) rather than –ise for verbs (and corresponding nouns etc.) derived from Greek –izein or Latin –izare, and for words modelled on these forms.'

CASE AUTH/2333/7/10

ANONYMOUS v BAYER

Promotion of Levitra

An anonymous and non contactable complainant complained about a four page document entitled 'Prescribing Policy: Vardenafil as first choice for erectile dysfunction' which stated that it was supported by an educational grant from Bayer Schering Pharma. Bayer Schering Pharma marketed Levitra (vardenafil).

The document briefly discussed the prevalence, cause and general treatment of erectile dysfunction and thereafter discussed Levitra in relation to national clinical guidelines, its evidence base and comparative cost savings.

The complainant stated that he had received the document unsolicited with no prescribing information enclosed. The top of page two clearly referred to Levitra and its licensed indication.

The detailed response from Bayer is given below.

The Panel noted that the document made very positive clinical and cost claims about vardenafil. A statement at the bottom of the front page included 'Supported by an educational grant from Bayer Schering Pharma. No editorial input from Bayer Schering Pharma ….'. Eight authors were listed on the back page. The Panel noted Bayer's submission that the mailing was initiated by a third party consultancy, and that it had no input into the content of the document. The Panel noted that whether a company was responsible for sponsored material depended on a number of factors. That the material was initiated by a third party did not, in itself, absolve the company from responsibility under the Code.

The Panel considered that there was no arm's length arrangement between the provision of the sponsorship and the generation of the prescribing policy. Bayer had accepted the consultancy's commercial proposal to write, secure named authors for, and publish guidance on the use of Levitra. The extract of the agreement between Bayer and the consultancy provided that the consultancy must ensure that the policy document was acceptable, *inter alia,* to Bayer. It thus appeared that, contrary to Bayer's submission, it had editorial control. The agreement and the overall arrangements were such that the consultancy had, in effect, operated as the company's agent in the generation of the material and Bayer was thus responsible for its content.

The Panel was very concerned about Bayer's submission that as the material was distributed to medicines managers who were not health professionals *per se* the material was not promotional. The Panel considered that this demonstrated a fundamental lack of understanding of the relevant requirements of the Code. The Code applied not only to material/activity directed at health professionals, but also appropriate administrative staff. Medicines could thus be promoted to medicines managers who were not health professionals so long as the material was relevant to their role and otherwise complied with the Code. The status of the intended audience was relevant but did not in itself determine whether or not the material was promotional; all the circumstances had to be taken into account. Promotion was defined in the Code as any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines.

The Panel noted that the agreement between the parties listed two objectives: to place Levitra as first choice phosphodiesterase inhibitor with primary care organisations and to advocate switches from other phosphodiesterase inhibitors to Levitra. The Panel noted that the material contained very positive clinical and cost claims for Levitra; Bayer had provided the consultancy with a vardenafil price list. The Panel considered that Bayer's submissions that the material was simply distributed on behalf of the authors and that the consultancy requested that the material be so distributed was not an accurate reflection of the arrangements as set out in the agreement. It was envisaged in the agreement at the outset that the material would be distributed by Bayer in the field. This implied promotional use. The mailing list was requested by and screened by Bayer. In the Panel's view the overall arrangements and content of the material were such that it was clearly promotional. The material ought to have borne prescribing information as referred to by the complainant. A breach of the Code was ruled.

During its consideration of this case the Panel was very concerned that the company's response and the overall arrangements demonstrated a fundamental lack of understanding of the requirements of the Code and a lack of control of promotional material. The Panel found it difficult to understand how the material could be seen as anything other that promotional material for which the company was responsible.

The Panel was extremely concerned about the content of the document. The title 'Prescribing Policy: Vardenafil as first choice for erectile dysfunction' implied that Levitra was 'the first choice' which was unacceptable under the Code. The Panel further noted that the document

variously described Vardenafil as a 'safe option' and that it had proven or demonstrated 'efficacy and safety'. All of these claims were contrary to the requirements of the Code which stated, *inter alia*, that the word 'safe' must not be used without qualification. The bullet point 'According to NICE [National Institute for Health and Clinical Excellence] guidance for Type 2 Diabetes vardenafil should therefore become the preferred prescribing option for erectile dysfunction;' implied that NICE had specifically recommended Levitra and that was not so. NICE recommended choosing the medicine with the lowest acquisition cost. The Panel noted that the sole allegation concerned the absence of prescribing information.

Taking all the circumstances into account the Panel decided that the company's conduct in relation to the Code warranted consideration by the Code of Practice Appeal Board and it decided to report the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for it to consider whether further sanctions were warranted.

The Appeal Board considered that Bayer's failure to recognise that the document was in fact wholly unacceptable promotional material was a shocking error of judgement. The Appeal Board was extremely concerned about the content of the document and about Bayer's arrangements. In that regard the Appeal Board noted that Bayer had not provided a copy of the full agreement between it and the consultancy. The Appeal Board considered that the overall arrangements and content of the material demonstrated a fundamental lack of understanding of the requirements of the Code.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of Bayer's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. In addition the Appeal Board decided, given the large number of medicines managers who had been sent the prescribing policy document, that Bayer should take steps to recover the item by writing to each recipient to ask them to, where practicable, return it. This should be done as soon as possible. The Appeal Board requested that the content of the letter be agreed with the Authority before it was sent; the letter should explain the reasons for the Appeal Board's decision. The progress of the steps to recover the document would be discussed at the audit.

On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the October 2010 audit report the Appeal Board was extremely concerned that Bayer had circulated the material at issue more widely than previously indicated to the Panel and the Appeal Board. The company apologised for the error and explained that it had come to light as a result of the requirement that the material be recovered from those to whom it had been sent. The Appeal Board considered that it was vital that responses to the Authority were accurate and gave complete information. The failure to provide comprehensive information was unacceptable. The Appeal Board noted Bayer's submission that the late notification was due to poor communication between the senior managers involved in preparing the response to the PMCPA. The Appeal Board decided that Bayer should be publicly reprimanded for this failure.

The Appeal Board noted Bayer's response that it would implement the recommendations in the report as soon as possible and that it had appointed a corrective and preventive action team to do this. The Appeal Board was concerned about the profile of the medical department with regard to compliance issues and considered that it should be raised.

The Appeal Board was concerned about the audit report particularly given that the company had been audited twice in 2007 as a result of another case. The Appeal Board decided that a further audit should be carried out in February 2011. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the February 2011 audit report, the Appeal Board noted the progress made since the audit in 2010. It was important that this progress was continued and maintained. The Appeal Board decided that no further action was required.

An anonymous and non contactable complainant submitted a four page document entitled 'Prescribing Policy: Vardenafil as first choice for erectile dysfunction' which stated that it was supported by an educational grant from Bayer Schering Pharma. Bayer Schering Pharma marketed Levitra (vardenafil).

The document briefly discussed the prevalence, cause and general treatment of erectile dysfunction and thereafter discussed Levitra in relation to national clinical guidelines, the National Institute for Health and Clinical Excellence (NICE), its evidence base and comparative cost savings.

COMPLAINT

The complainant stated that he had received the document unsolicited, post marked 'Reading' with no prescribing information enclosed. The top of page two of the mailing made clear reference to Levitra and its licensed indication.

The detailed response from Bayer is given below.

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

RESPONSE

Bayer explained that the material was initiated by a

third party consultancy as a result of its proposal to write an information document drawing the attention of medicines managers engaged in primary care organisations (PCOs) to NICE guidance regarding the prescribing of phosphodiesterase-5 (PDE5) inhibitors for type 2 diabetics with erectile dysfunction. The cost of such prescriptions was reimbursable under Schedule 2. The NICE guidance was that the PDE5 inhibitor to be prescribed in the first instance should be that with the lowest cost. Due to a recent price change, the lowest cost PDE5 inhibitor was vardenafil and the independent group which produced the prescribing policy, cited that its prescription could potentially make a maximum cost saving per 100,000 population of £38,120.

Bayer stated that it provided financial support to the consultancy for the writing of the material at issue.

The purpose of the document was to provide information for medicines managers in PCOs that would enable PCOs and trusts to make cost savings and help the NHS face its financial challenge of the efficiency savings required by 2013/14.

It was considered that the communication of information regarding NICE guidance and the significant change to an existing medicine, namely the cost reduction of vardenafil, would help primary care trusts (PCTs) with their budgets. The distribution of the document was not intended to be a means of promoting Levitra to health professionals.

Bayer distributed the document on behalf of the independent authors to 1,665 medicines managers, engaged in PCOs. The mailing addresses were provided by a third party provider. Particular care was taken so that these PCO medicines managers would receive the document. In some cases such managers might also be clinicians and so the mailing list was purposefully screened to ensure that the document was addressed to individuals in their capacity as medicines managers. This was done so that the distribution would not be to health professionals *per se* and therefore constitute promotion.

Bayer stated that it had no input into the content of the prescribing policy.

Bayer explained that the consultancy coordinated and facilitated the writing by an independent group of non-clinical authors who were medicines managers in PCOs. Bayer provided financial support but had no influence in the selection of the authors.

The prescribing policy document was an information piece and it was never intended to use it for the purposes of promotion but only to assist PCTs with efficiency savings and budget forecasts. Nor was it intended that this information piece should be adapted in any way to make it a promotional item. For this reason prescribing information was not and could not be added to it. Bayer submitted that the addition of prescribing information to the policy document would have rendered it promotional.

Given that the document was purely for the information of medicines managers engaged in PCOs and was not to be used as a means of promotion to health professionals it was not certified. Consequently there was no certificate of approval. It was simply distributed on behalf of the authors.

The policy document was an information piece which was for, and sent, only to those to whom the information was relevant, namely medicines managers, and not health professionals *per se*.

In response to a request for further information Bayer provided an extract from a letter dated 9 April 2010 to Bayer from its consultancy. It outlined a proposal to produce guidance on the use of vardenafil (prescribing policy document).

The product manager responded to the letter by telephone. A further letter (dated 19 April 2010) from the consultancy formed the basis of the agreement between it and Bayer. Given that the vardenafil policy document was independently written there was no agreement between Bayer and the authors.

Bayer did not provide any product or other information for the authors of the prescribing policy. However Bayer provided its consultancy with a list of the new vardenafil prices.

The consultancy coordinated and facilitated the writing of the prescribing policy document entirely by email. There were no meetings or advisory boards held. The consultancy knew that all the authors had an interest in cost effective prescribing and were engaged in PCOs. The authors were not brought together as a group. A first draft was prepared by the lead author, a head of medicines management, at a named PCT, and circulated by email to the other authors for a series of reviews so that their comments could be incorporated.

The consultancy advised Bayer two years ago about rivaroxaban activities and in 2010 and gave a lecture on PCOs and practice-based prescription groups at an internal Bayer Schering Pharma meeting, it had raised awareness amongst PCTs that had ScriptSwitch to highlight vardenafil as the lowest cost PDE5 inhibitor in line with NICE guidelines.

A thorough analysis of the company's contract database showed that none of the authors had provided any sort of consultancy service to Bayer.

Bayer stated that it received a copy of the final draft from the consultancy on 5 July 2010; one minor typographical error was brought to its attention. Bayer had no editorial input into the document and did not comment on it.

Bayer submitted that the consultancy requested that

the Levitra prescribing policy document should be mailed on behalf of the authors. It was publicised by a mailing in order that the information was made known only to those for whom it was directly relevant ie medicines managers. Again, the prescribing policy document was an information piece and it was never intended to be used for promotional purposes but only to assist PCTs with efficiency savings and budget forecasts. To have publicised the prescribing policy document, for example, as an article or supplement even in a journal with a target audience specifically intended to include medicines managers would have placed it in the public domain. Consequently it would have been potentially accessible to health professionals and members of the public and, as such, the policy would have been promotional.

Bayer asked a third party to provide a list of people involved in medicines management. Given that it was critical that the prescribing policy should only be sent to medicines managers for whom it was directly relevant, in order to assist them in managing budgets and encourage cost effective prescribing, Bayer screened the mailing list rather than delegate the task to a third party service supplier. This was to ensure that it only included recipients who had a medicines management function.

A copy of the envelope was provided. Bayer submitted that there was no accompanying material; the envelope contained only the Levitra prescribing policy and the recipient's address.

PANEL RULING

The Panel noted that the document entitled 'Prescribing Policy: Vardenafil as first choice for erectile dysfunction' made very positive clinical and cost claims about the product. A statement at the bottom of the front page read 'Supported by an educational grant from Bayer Schering Pharma. No editorial input from Bayer Schering Pharma. Date of preparation July 2010'. Eight authors were listed on the back page. The Panel noted Bayer's submission that the mailing was initiated by a third party, a consultancy, and that it had no input into the content of the prescribing policy. The Panel noted that whether a company was responsible for sponsored material depended on a number of factors. That the material was initiated by a third party did not, in itself, absolve the company from responsibility under the Code for its content.

It had previously been decided in relation to material aimed at health professionals that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable it if had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes. The Panel considered that this statement of principle applied equally to the content of sponsored material aimed at appropriate administrative staff.

The Panel considered that there was no arm's length arrangement between the provision of the sponsorship and the generation of the prescribing policy. The consultancy had sent Bayer a commercial proposal to write, secure named authors for, and publish guidance on the use of Levitra which the company had decided to accept. The Panel noted that it had only been provided with an extract of the agreement between Bayer and the consultancy. Contrary to Bayer's submission that it had no editorial input into the document and did not comment on it, the letter, which formed the basis of the agreement provided that the consultancy must ensure that the policy document was acceptable, *inter alia*, to Bayer. It thus appeared that Bayer had editorial control. The agreement and the overall arrangements were such that the consultancy had, in effect, operated as the company's agent in the generation of the material and Bayer was thus responsible for its content. The Panel considered that this was so irrespective of the subsequent distribution of the material.

The Panel was very concerned about Bayer's submission that as the material was distributed to medicines managers who were not health professionals *per se* the material was not promotional. The Panel considered that this demonstrated a fundamental lack of understanding of the relevant requirements of the Code. The Code applied not only to material/activity directed at health professionals, but also appropriate administrative staff (Clause 1.1 refers). Medicines could thus be promoted to medicines managers who were not health professionals so long as the material was relevant to their role and otherwise complied with the Code. The status of the intended audience was relevant but did not in itself determine whether or not the material was promotional; all the circumstances had to be taken into account. Promotion was defined in Clause 1.2 as any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines.

The Panel noted that the agreement between the parties listed two objectives: to place Levitra as first choice phosphodiesterase inhibitor with PCOs and to advocate switches from other phosphodiesterase inhibitors to Levitra. The Panel noted that the material contained very positive clinical and cost claims for Levitra; Bayer had provided the consultancy with a vardenafil price list. The Panel considered that Bayer's submissions that the material was simply distributed on behalf of the authors and that the consultancy requested that the material be so distributed was not an accurate

reflection of the arrangements as set out in the agreement. It was envisaged in the agreement at the outset that the material would be distributed by Bayer in the field. This implied promotional use. The mailing list was requested by and screened by Bayer. In the Panel's view the overall arrangements and content of the material were such that it was clearly promotional. The material ought to have borne prescribing information as referred to by the complainant. A breach of Clause 4.1 was ruled.

During its consideration of this case the Panel was very concerned that the company's response and the overall arrangements demonstrated a fundamental lack of understanding of the requirements of the Code and a lack of control of promotional material. The Panel found it difficult to understand how the material could be seen as anything other that promotional material for which the company was responsible.

The Panel queried Bayer's submission that there was no accompanying material and the envelope contained only the prescribing policy and the recipient's address. The envelope provided by Bayer, however, was a plain window envelope and thus it appeared that there should have been some other material inside the envelope which bore the recipient's address. The position was unclear.

The Panel was extremely concerned about the content of the document. The title 'Prescribing Policy: Vardenafil as first choice for erectile dysfunction' implied that Levitra was 'the first choice' to treat erectile dysfunction and this implication was unacceptable in relation to the requirements of Clause 7.10 of the Code. The Panel further noted that the summary stated that 'Vardenafil offers an effective, well-tolerated and safe option for the treatment of ED'. A bullet point on page 1 stated '[Vardenafil has] proven efficacy and safety' and another bullet point on page 3 stated 'Vardenafil has demonstrated efficacy and safety'. All of these claims were contrary to the requirements of Clause 7.9 which stated, *inter alia*, that the word 'safe' must not be used without qualification. The bullet point 'According to NICE guidance for Type 2 Diabetes vardenafil should therefore become the preferred prescribing option for erectile dysfunction;' which appeared as part of the Executive Summary on the front page implied that the NICE guidance at issue had specifically recommended Levitra and that was not so. NICE recommended choosing the medicine with the lowest acquisition cost. The Panel noted that the sole allegation concerned the absence of prescribing information.

The Panel noted that it had been provided with part of the agreement that discussed the activity at issue. The Panel considered that Bayer would be well advised to revisit the entire agreement to ensure that any outputs were Code compliant.

Taking all the circumstances into account the Panel decided that the company's conduct in relation to the Code warranted consideration by the Code of Practice Appeal Board and it decided to report the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for it to consider whether further sanctions were warranted.

COMMENTS FROM BAYER

Bayer accepted the Panel's ruling of a breach of Clause 4.1 and, furthermore, that the Panel found that the document would also have been in breach of Clause 7.9 and 7.10. Consequently Bayer apologised to the Authority for this failure of compliance and extended its apologies to the Appeal Board.

Bayer appreciated that this most unfortunate of incidents led to the Panel's concern that it represented a fundamental lack of understanding of the requirements of the Code and a lack of control of promotional material.

Bayer submitted that corporate compliance was of the utmost importance to it. To this end Bayer had a medical governance group and compliance infrastructure designed to prevent such regrettable incidents. Bayer also retained the services of an external compliance consultancy. Nonetheless, on this occasion there had clearly been a fundamental lack of judgement and lack of process control. Bayer recognised the seriousness of this failure of compliance and therefore had undertaken a number of actions:

- The general business unit (business unit head, medical and marketing), medical group and medical governance had met to thoroughly review the case in order to understand how these non-compliant events came about and to prevent future re-occurrences.

- The business unit would formally review medical and educational goods and services and contracts procedures in September 2010.

- An external compliance agency would audit Bayer in September 2010.

- An internal communication had been sent to all business units, including their sales representatives, requiring confirmation that they had read and understood the findings of the Panel in this case. This was being reinforced by the relevant managers addressing the issue directly with their reportees. The communication emphasised the following:

    - The content of an item and the use made of it determined whether or not it was promotional irrespective of the role of the individuals to whom it was targeted.

    - Mailings undertaken on behalf of third parties must be certified in accordance with Bayer's standard operating procedure on Certification of Promotional Items, Non-Promotional Items

and Activities in the same way as any other mailings or activities conducted by Bayer.

Bayer trusted that its submission demonstrated the seriousness with which it regarded this matter and, importantly, that the necessary and appropriate actions had been taken.

Finally, Bayer reiterated its apologies to both the Panel and Appeal Board and emphasised that every endeavour was being made in order to ensure that there was no future recurrence.

APPEAL BOARD CONSIDERATION

The Appeal Board considered that Bayer's failure to recognise that the prescribing policy document was in fact wholly unacceptable promotional material was a shocking error of judgement. The Appeal Board was extremely concerned about the content of the document and about Bayer's arrangements with the consultancy. In that regard the Appeal Board noted that Bayer had not provided a copy of the full agreement between it and the consultancy. The Appeal Board considered that the overall arrangements and content of the material demonstrated a fundamental lack of understanding of the requirements of the Code.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of Bayer's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. In addition the Appeal Board decided, given the large number of medicines managers who had been sent the prescribing policy document, that Bayer should take steps to recover the item by writing to each recipient to ask them to, where practicable, return it. This should be done as soon as possible. The Appeal Board requested that the content of the letter be agreed with the Authority before it was sent; the letter should explain the reasons for the Appeal Board's decision. The progress of the steps to recover the document would be discussed at the audit.

On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

FURTHER APPEAL BOARD CONSIDERATION

Upon receipt of the October 2010 audit report the Appeal Board was extremely concerned that Bayer had circulated the material at issue more widely than previously indicated to the Panel and the Appeal Board. The company apologised for the error and explained that it had come to light as a result of the requirement that the material be recovered from those to whom it had been sent. The Appeal Board considered that it was vital that responses to the Authority were accurate and gave complete information. The failure to provide comprehensive information was unacceptable. The Appeal Board noted Bayer's submission that the late notification was due to poor communication between the senior managers involved in preparing the response to the PMCPA. The Appeal Board decided that Bayer should be publicly reprimanded for this failure.

The Appeal Board noted Bayer's response that it would implement the recommendations in the report as soon as possible and that it had appointed a corrective and preventive action team to do this. The Appeal Board was concerned about the profile of the medical department with regard to compliance issues and considered that it should be raised.

The Appeal Board was concerned about the audit report particularly given that the company had been audited twice in 2007 as a result of another case. The Appeal Board decided that a further audit should be carried out in February 2011. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the February 2011 audit report, the Appeal Board noted the progress made since the audit in 2010. It was important that this progress was continued and maintained. The Appeal Board decided that no further action was required.

Complaint received	**15 July 2010**
Undertaking received	**8 September 2010**
Appeal Board consideration	**22 September 2010, 10 November 2010, 17 March 2011**
Interim case report published	**29 October 2010**
Case completed	**17 March 2011**

CASE AUTH/2352/8/10

GLAXOSMITHKLINE v CHIESI

Clinical Support Service

GlaxoSmithKline alleged that Chiesi had facilitated a switch service rather than a genuine therapeutic review. This was specifically prohibited under the Code. GlaxoSmithKline considered that the service did not offer a comprehensive range of relevant treatment choices, but was limited by the prescribing instructions given to practices by the local primary care pharmacy services and that Chiesi was aware of these instructions but continued to support the implementation. GlaxoSmithKline also considered that the clinical assessments carried out by the pharmacists employed by Chiesi were inadequate to ensure that patient care was enhanced or maintained.

GlaxoSmithKline obtained evidence of this activity from a letter sent by a GP to a patient which stated:

> **'We are currently carrying out a review of our patients on Seretide 125 Evohalers. I would like to advise you that our practice policy has recently been changed and that from now on we will be prescribing Fostair 100/6 inhalers instead.'**

The letter reassured the patient regarding the change and offered an appointment if needed, thus it was apparent that no discussion with the patient had taken place as part of a clinical review, and the change was initiated without informed consent. The footer on the letter made it clear that this review had taken place under the auspices of 'A therapeutic review service provided as a service to medicine by Chiesi Limited'.

GlaxoSmithKline submitted that the letter clearly suggested that patients were switched from Seretide 125 Evohaler to Fostair 100/6 inhaler due to a change in 'practice policy', rather than a clinical assessment of individual patient's needs. As such GlaxoSmithKline believed that Chiesi had supported a switch service rather than a genuine therapeutic review of asthma patients. Further, GlaxoSmithKline submitted that in inter-company correspondence the review implemented by Chiesi appeared to be a notes review which, for the treatment of asthma, did not represent good clinical practice (Thomas *et al* 2009, Doyle *et al* 2010).

GlaxoSmithKline also provided a copy of an email from the local health board to practice managers which encouraged GP practices to take up Chiesi's offer of a 'therapeutic review' service and detailed three areas of prescribing covered by Chiesi's service. A comprehensive range of therapeutic options was not listed as required by the Code to ensure a genuine therapeutic review. Chiesi informed GlaxoSmithKline that it had received a copy of this email from the primary care trust (PCT) and so knew of the very limited therapeutic options being recommended yet continued to facilitate this service. The email listed the product/s that patients could be transferred to.

GlaxoSmithKline alleged that as the choice of medicines to be used following the reviews was very limited, the services could not be true therapeutic reviews.

Furthermore, GlaxoSmithKline considered that a *bona fide* therapeutic review should be closely aligned to best practice guidelines in a particular therapy area. Therefore a therapeutic asthma review should closely follow the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guidelines, which were generally considered to represent best practice in asthma management. Patients who currently received Seretide 125 were already at step 3 (of 5) of these guidelines and had moderately severe disease which required careful clinical assessment to ensure optimal treatment of what was a potentially life-threatening condition. The guidelines stipulated that 'All people with asthma should have access to primary care services delivered by doctors and nurses with appropriate training in asthma management' and that in a structured review 'All patients should be reviewed regularly by a doctor or nurse with appropriate training in asthma management. The review should incorporate a written action plan'. The use of pharmacists to conduct the 'clinical assessment' of these patients was at odds with this recommendation as was the lack of any written action plan.

The guidelines also focussed on identifying patients whose asthma was under- or over-treated and increasing or decreasing their treatments in line with a well-defined treatment ladder. The Chiesi service, as described in the email, focussed solely on switching patients between different medicines on the same rung of the treatment ladder. Such switches were not recommended within the BTS/SIGN guidelines.

GlaxoSmithKline considered that Chiesi's admitted knowledge of the content of the email to practices from the local NHS meant it knew about the limited therapeutic options being recommended for its Clinical Support Service (CSS) but continued to support and facilitate the prescription changes which thus made it responsible under the Code. The clinical assessments carried out for moderately severe asthma patients were inadequate. Given these concerns, GlaxoSmithKline believed that Chiesi's CSS was a switch programme that failed to

maintain high standards and might impact on patient safety and the reputation of the pharmaceutical industry contrary to Clause 2.

The detailed response from Chiesi is given below.

The Panel noted Chiesi's submission that the CSS had assisted the local health board, under an arrangement akin to a joint working partnership, for a number of years. Chiesi had referred to the ABPI guidance notes on joint working between pharmaceutical companies and the NHS. In the Panel's view the CSS was service provision, not joint working. Joint working covered situations where, for the benefit of patients, the NHS and one or more pharmaceutical companies pooled skills, experience and/or resources with a shared commitment to successful delivery of patient centered projects. Each party had to make a significant contribution and outcomes had to be measured. Treatments must be in line with nationally accepted clinical guidance where such existed and the arrangements between the parties must be open and transparent.

The Panel noted that GlaxoSmithKline had alleged that the current service, a review based on patients' medical records, was insufficient to enhance patient care or benefit the NHS and maintain patient care.

The Clinical Support Service Protocol explained that the service would enable primary care organisations and individual practices to carry out clinical assessments and therapeutic reviews of specific patient groups. The service was non promotional and non product specific. The GP retained full control of the process at all times.

The SOP Procedure for Asthma Therapeutic Review began by referring to asthma control and the BTS/SIGN guidelines 2008. The introduction stated that when deemed necessary, an asthma clinic could be used to optimise patients' asthma control and provide reinforcement and education on the importance and achievability of good asthma control and hence improve quality of life. The CSS pharmacist would clarify with the GP whether the review was conducted with or without the patient. Factors which determined this included whether after clinical assessment any potential changes to a patient's asthma treatment might result in a change of molecule or device but would ultimately be determined by the GP's instructions. If the GP chose a paper review the Asthma Therapeutic Review Authorization Form (Non-Clinic) would be completed and identify: which patient groups should be reviewed; what the GP's treatments of choice were; which strengths should be used and any special instructions. The form stated that patients would be reviewed in accordance with BTS and National Institute for health and Clinical Excellence (NICE) Guidelines. Products were listed beneath the following headings: short-acting beta$_2$ agonists, long acting beta$_2$ agonists, inhaled corticosteroids, fixed inhaled corticosteroids/long-acting beta-agonist (ICS/LABA) combinations and others.

The Therapeutic Review Project Specification Form set out the services to be provided to the GP practice and the terms of service of a patient record review. It was noted that the result of a clinical assessment might require a face-to-face clinical assessment, possible changes in treatment including changes of dose, medicine or cessation of treatment. No medicines would be changed unless authorized by the GP or if, in the clinical judgement of the pharmacist, there was a query which required resolution or discussion by or with the GP. The GP and pharmacist would meet at the end of each working day and at the end of the review so, *inter alia*, the GP could summarize the completed work and authorize any further actions required. The authorizing GP was asked to sign each page of the patient lists to indicate that they were 'fully happy' with the action taken.

The Panel noted that GlaxoSmithKline had provided a patient letter dated 5 October 2009 to support its allegations about the current service. The Panel noted that the standard operating procedure (SOP) contemporaneous to the patient letter appeared to describe a different service, it was dated 2 April 2009. It described a review based on clinical assessment of a patient's records alone. There was no reference to a patient clinic. The GP authorized each step. The Panel did not have all the documentation for this review but considered that GlaxoSmithKline had not made specific allegations about it. In the Panel's view, the only issue to consider was whether a medical record review was adequate to, *inter alia*, enhance or maintain patient care.

The Panel noted that Thomas *et al* was a 2 year retrospective matched cohort study which evaluated the impact on asthma control of inhaler device switching without an accompanying consultation in general practice and determined that such a switch was associated with worsening asthma control. Doyle *et al* undertook qualitative interviews with 19 asthma patients who had experienced a non-consented switch of their inhaler device and concluded that such switches may, *inter alia*, diminish self-control associated with good asthma management. The Panel noted that there was some evidence in relation to changing a patient's device without consent. No clinical evidence had been submitted in relation to other changes such as a change in molecule, dose, etc. The Panel noted, however, that the CSS, based on patients' records, could potentially involve a change of device.

The Panel noted GlaxoSmithKline further considered that a *bona fide* therapeutic review should be closely aligned to BTS/SIGN best practice guidelines. As an example GlaxoSmithKline noted that moderately severe asthmatics on Seretide 125 were already at step 3 (of 5) of the BTS guidelines and required careful clinical assessment. The guidelines referred to access to primary care services delivered by doctors and nurses with appropriate training in asthma management and GlaxoSmithKline alleged

that the use of pharmacists was at odds with this recommendation as was any written action plan. The Panel noted the BTS/SIGN guidelines and reference to clinical review by a nurse or doctor. The Panel noted that the guidelines were referred to in the introduction to the current SOP. The Panel did not consider that a medical record review by a pharmacist as part of the CSS meant that ongoing clinical care from a nurse or doctor was in any way precluded as implied by GlaxoSmithKline.

The Panel noted the SOP training document for pharmacists. The decision to have a medical notes review or clinic was taken by the authorizing GP. The SOP Procedure for Asthma Therapeutic Review and the SOP Training Document for Pharmacists made it clear that in some circumstances a clinic review might be preferable.

The authorizing GP defined the scope of the review, identified appropriate patients and had the final word on all matters in relation to it including product changes. In such circumstances the Panel did not consider that on the information before it about the current service a review of patients' records by a pharmacist in principle failed to enhance patient care or benefit the NHS and maintain patient care as alleged. No breach of the Code was ruled. The Panel consequently ruled no breach of Clause 2.

The Panel noted that the email from the local NHS primary care pharmacy services encouraged practices to take up the assistance of the CSS to complete the three tasks outlined in the email. The first task was to review patients using CFC containing beclometasone inhalers and transfer them to CFC-free inhalers. The local formulary options were listed – Clenil modulite or Qvar for adults over 12 and Clenil Modulite for children. The second review was of Seretide 125 MDI patients with a possibility of transfer to Fostair MDI which was described as a local formulary option and a cost effective alternative to Seretide 125 MDI. The final option described assistance to optimize the prescribing of tramadol to the formulary preferred option of Maxitram SR.

The Panel accepted, in general, that when *bona fide* therapeutic reviews were offered to practices the prescriber would, nonetheless, be aware which products were on the local formulary and he/she might decide, as a result of the review, that such products were suitable therapeutic options. However, in the view of the Panel, the content of the service and way it was offered must comply with the Code. Irrespective of what products were on the local formulary the review must offer the prescriber a comprehensive range of treatment choices. Pharmaceutical company assistance in the implementation of a switch service was unacceptable.

In the view of the Panel the email to practices from the local primary care pharmacy services was such that the prescriber's choice was, in effect, restricted to switching to those products mentioned therein. Practices would attach the greatest weight to the email. It was entirely unclear from Chiesi's responses what it knew about how the service would be introduced to local practices at the outset by the local health board other than such instruction would be by email. The Panel considered that on receipt of a copy of the email Chiesi knew that the local primary care pharmacy services was encouraging GPs to use its service in a way that rendered its provision in breach of the Code. That the email was sent independently and that Chiesi submitted that it had no prior knowledge of its content before it received a confidential copy was irrelevant. Once Chiesi knew about the email then it also knew that GPs were being encouraged to use the CS service to effect a switch programme. This was compounded by the wholly unacceptable provision by Chiesi of the email and the company's response to the local CSS pharmacist. The Panel had not seen the covering email provided to the local CSS pharmacist. Nonetheless it appeared that the local CSS pharmacist might have in effect been instructed to implement a switch service. Overall, the Panel considered that the arrangements did not meet the requirements of the Code and a breach was ruled, which was upheld on appeal by Chiesi. High standards had not been maintained. A breach of the Code was ruled which was upheld on appeal by Chiesi. The Panel considered that the provision of a switch service brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled which was upheld on appeal by Chiesi.

GlaxoSmithKline UK Ltd complained about a Clinical Support Service (CSS) run by Chiesi Limited in one particular NHS area. Inter-company dialogue had failed to resolve the matter.

COMPLAINT

GlaxoSmithKline alleged that Chiesi had facilitated a switch service rather than a genuine therapeutic review in the local NHS area. This was specifically prohibited under the Code. GlaxoSmithKline considered that the service did not offer a comprehensive range of relevant treatment choices, but was limited by the prescribing instructions given to practices by the local primary care pharmacy services and that Chiesi was aware of these instructions but continued to support the implementation. GlaxoSmithKline also considered that the clinical assessments carried out by the pharmacists employed by Chiesi were inadequate to ensure that patient care was enhanced or maintained.

GlaxoSmithKline obtained evidence of this activity from a letter sent by a GP to a patient which informed them of a switch of their inhaler as part of 'A therapeutic review service provided as a service to medicine by Chiesi Limited' and from an email from the local health board which encouraged GPs to take up Chiesi's offer of a 'therapeutic review' service and detailed the areas of prescribing covered by Chiesi's service. A comprehensive range

of therapeutic options was not listed as required by the Code to ensure a genuine therapeutic review. Chiesi informed GlaxoSmithKline that it had received a copy of this email from the primary care trust (PCT) and so it knew about the very limited therapeutic options being recommended yet continued to facilitate this service.

GlaxoSmithKline understood that similar activity was taking place in other parts of the country.

Letter

This letter, dated 5 October 2009, sent by a GP practice to a patient, stated:

'We are currently carrying out a review of our patients on Seretide 125 Evohalers. I would like to advise you that our practice policy has recently been changed and that from now on we will be prescribing Fostair 100/6 inhalers instead.'

The letter reassured the patient regarding the change and offered an appointment if needed, thus it was apparent that no discussion with the patient had taken place as part of a clinical review, and the change was initiated without informed consent. The footer on the letter made it clear that this review had taken place under the auspices of 'A therapeutic review service provided as a service to medicine by Chiesi Limited'.

In inter-company correspondence Chiesi stated that 'The pharmacist will assess individual patient records and carry out a full clinical assessment of each patient's medicine(s) and medicine history prior to any therapy review taking place'. Chiesi stated that when its pharmacists provided the CSS they:

- Assessed each patient's medicine(s) to ensure any therapy review requested and authorised by the GP was appropriate
- Checked for medicine interactions
- Checked for over or under ordering of medicines
- Checked for duplicate therapies
- Assessed compliance issues
- Assessed dosages and strengths to ensure they were correct
- Checked licensed indications
- Reviewed quantities issued and identified in-equivalence of quantities
- Checked all clinical investigations were up-to-date and identified any tests which were overdue or not recorded
- Assessed potential side effects
- Assessed possible strength optimisation.

None of the above referred to any discussion with the patient about their condition, but were, in effect, a notes review. For the treatment of asthma, a potentially life-threatening condition, this was inadequate and did not represent good clinical practice. A 2 year, retrospective, cohort study by Thomas *et al* (2009) showed that patients whose asthma medicine was switched without their consent experienced worse asthma control; patients were significantly more likely to experience unsuccessful treatment and significantly less likely to experience successful treatment than patients who were not switched without consent. The authors concluded that switching without face-to-face discussion was inadvisable. Doyle *et al* (2010) also highlighted the need for clear and open communication with patients, as switching inhalers without consent could reduce their confidence in asthma medicine and perception of control over their disease. The Code required that therapy reviews must enhance or at least maintain patient care, but the lack of one-to-one clinical discussion with the patient about their asthma treatment before treatment change meant that this tenet was not observed.

The letter clearly suggested that patients were switched from Seretide 125 Evohaler to Fostair 100/6 inhaler due to a change in 'practice policy', rather than a clinical assessment of individual patient's needs. As such GlaxoSmithKline believed that Chiesi had supported a switch service rather than a genuine therapeutic review of asthma patients.

Email

GlaxoSmithKline submitted that the document provided was part of an email sent to practice managers by the local health board. It stated that Chiesi would support therapeutic review services in three specific areas and urged practices to take up Chiesi's offer to review the following:

1 Asthma patients who used CFC-containing beclomethasone inhalers with a view to switching them to CFC-free devices the choice of which was limited to either Clenil Modulite (a Chiesi product) or Qvar for adults and solely to Clenil Modulite for patients below the age of 12.

2 Patients who used Seretide 125 Evohaler 'with possibility to transfer to Fostair MDI' (a Chiesi product).

3 Patients on various modified-release formulations of tramadol, with a view to switching them to Maxitram SR, (a Chiesi product), the local formulary preferred option.

GlaxoSmithKline alleged that as the choice of medicines to be used following the above reviews was very limited, the services could not be true therapeutic reviews. Clearly a PCT or health board might ask practices to engage in wholesale switching, and companies might promote simple switching from one product to another, but it was unacceptable for a pharmaceutical company to facilitate that switching even by means of a third party such as a sponsored nurse.

The Chiesi CSS had been the subject of two previous cases; in Case AUTH/2097/2/08 a competitor complained and in Case AUTH/2103/3/08

an anonymous PCT member complained. In both cases the Panel found no breach of the Code. In the first case the competitor company submitted two pharmacist forms from the CSS pharmacist indicating there was likely to be an increased use of Clenil Modulite (the Chiesi CFC-free pMDI) and a corresponding decrease in use of CFC-containing beclomethasone pMDIs. The Panel considered on the basis of the limited evidence before it that there was no evidence to show that the service as a whole was limited to Trinity-Chiesi products or that any inducement had been offered or given.

In the second case, the complainant provided no documentary evidence but considered that changing from CFC-containing beclomethasone pMDIs to the Chiesi CFC-free beclomethasone pMDI was done without therapeutic review. CFC-containing pMDIs were being phased out so patients on those medicines would have to be transferred to others. Chiesi provided details of its CSS. The Panel was concerned that some examples of the patient letters appeared to indicate that as a result of the CSS patients would be changed to Trinity-Chiesi's product, but the complainant provided no evidence that the CSS was a switch service. The Panel ruled no breach.

GlaxoSmithKline submitted that its complaint was different as it provided evidence that Chiesi knew of the limited therapeutic options available to local GPs and the inadequacy of the review service for moderately severe asthma patients.

The Code made clear that for a therapeutic review service sponsored by a pharmaceutical company to be acceptable, a comprehensive range of treatments (including non-medicinal ones) must be available to the prescriber, not simply those of the sponsoring company. In inter-company correspondence, Chiesi asserted that each GP determined the 'medications to be considered based on the comprehensive range of medications which is available to him/her generally or from their own formulae'. However, the email to practice managers clearly stated which 'areas of prescribing can be covered by this external support service' and then gave very limited options for each of the three areas. Chiesi stated that it was sent a copy of this email 'in confidence directly from the local health board' and it had no input or prior knowledge of its content until its receipt. However, on its receipt, Chiesi then knew of the very limited options being made available to prescribers but continued to support and facilitate the prescription changes thus making it responsible under the Code.

The options available were not simply limited, they were predominantly Chiesi products:

For changing patients from CFC-containing inhalers they listed only two pressurised MDIs and omitted all the other non-CFC containing devices. For those under 12 years, they solely advised the use of the Chiesi pMDI. As this was not a comprehensive range of treatments, it was inappropriate for Chiesi to facilitate this programme.

The therapeutic review of asthma patients on Seretide 125 MDI was described as one with the 'possibility of transfer to formoterol/beclomethasone (Fostair) MDI' and went on to describe Fostair as a cost-effective option to Seretide 125 MDI. For this to be a valid therapeutic review service, there must also be the 'possibility of transfer to' any one of a comprehensive range of other treatment options. The intention of the letter appeared to be to direct practices to change patients from Seretide 125 MDI to Fostair MDI as a cost-saving exercise, rather than one that was patient-led to ensure each individual received optimal treatment after appropriate clinical assessment.

The final area of prescribing covered in the letter was 'to optimise prescribing of tramadol m/r formulations to the local preferred option – Maxitram SR', a Chiesi product. There were numerous tramadol products available and other therapeutic options for the same indications. Chiesi's facilitation of this prescribing change, even if there was clinical assessment, was in breach of the Code as no other therapeutic options were to be considered.

Furthermore, GlaxoSmithKline considered that a *bona fide* therapeutic review should be closely aligned to best practice guidelines in a particular therapy area. Therefore a therapeutic asthma review should closely follow the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guidelines, which were generally considered to represent best practice in asthma management. Patients who currently received Seretide 125 were already at step 3 (of 5) of these guidelines and had moderately severe disease which required careful clinical assessment to ensure optimal treatment of what was a potentially life-threatening condition. The guidelines stipulated that 'All people with asthma should have access to primary care services delivered by doctors and nurses with appropriate training in asthma management' and that in a structured review 'All patients should be reviewed regularly by a doctor or nurse with appropriate training in asthma management. The review should incorporate a written action plan'. The use of pharmacists to conduct the 'clinical assessment' of these patients was at odds with this recommendation as was the lack of any written action plan.

The guidelines also focussed on identifying patients whose asthma was under- or over-treated and increasing or decreasing their treatments in line with a well-defined treatment ladder. The Chiesi service, as described in the email, focussed solely on switching patients between different medicines on the same rung of the treatment ladder. Such switches were not recommended within the BTS/SIGN guidelines.

GlaxoSmithKline considered that Chiesi's admitted knowledge of the content of the email to practices from the local NHS meant it knew about the limited therapeutic options being recommended for its CSS

but continued to support and facilitate the prescription changes which thus made it responsible under the Code. GlaxoSmithKline also considered the clinical assessments carried out for moderately severe asthma patients were inadequate. Given these concerns, GlaxoSmithKline believed that Chiesi's CSS was a switch programme that failed to maintain high standards and might impact on patient safety and the reputation of the pharmaceutical industry in breach of Clauses 18.4, 9.1 and 2.

RESPONSE

Chiesi submitted that its CSS was a genuine therapeutic review service and not a switch service whereby a patient's medicine was simply changed to another without any clinical assessment.

In order to ensure the service complied with the Code all members of the CSS team who carried out therapeutic reviews were registered pharmacists who reported into a director who was also a registered pharmacist.

Therapeutic reviews were always done at the invitation and request of the GPs who decided which therapy areas should be reviewed and determined the medicines to be considered based on the comprehensive range available generally or from their own formulary. The CSS team did not influence, and was not permitted to be part of this decision making process. Once a GP had decided on a review, he/she could ask to be contacted by the CSS office if he/she wished to learn more about or potentially use the service. If the office agreed that Chiesi could support a particular request for a therapeutic review, in line with its standard operating procedure (SOPs), a CSS pharmacist would be allocated to undertake this review. In providing a therapeutic review, the pharmacist would operate under the written instructions of the GP. This written documentation explicitly detailed the therapy areas and medicine options the GP had selected.

Before any therapy review took place, the pharmacist would access individual patient records and clinically assess the full range of each patient's medicine and medicine history. As the recognised professional expert on medicines, the pharmacist did the following:

- Assessed each individual patient's medicine to ensure any therapy review requested and authorised by the GP was appropriate
- Checked for medicine interactions
- Checked for over or under ordering of medicines
- Checked for duplicate therapies
- Assessed compliance issues
- Assessed dosages and strengths to ensure they were correct
- Checked licensed indications
- Reviewed quantities issued and identified in-equivalence of quantities
- Checked all clinical investigations were up to date and identified tests overdue or not recorded
- Assessed potential side effects
- Assessed possible strength optimisation.

Chiesi noted that this was not an exhaustive list as different reviews might require additional considerations.

All clinical assessments, patient reviews and patient clinics were undertaken by the pharmacist on an individual patient basis, as detailed in the SOP. Any of the clinical queries or recommendations which emanated or resulted from these assessments, were detailed on a medicine query form and discussed and resolved at the end of each working day directly with the authorising GP. All individual patient reviews were signed off by the GPs, including any changes in treatment plans. As such, the GP retained full control of the review process, and the pharmacist worked under his/her instructions; the GP was fully responsible for any changes in individual treatment plans.

During inter-company dialogue GlaxoSmithKline did not appear to understand that Chiesi's pharmacists carried out a clinical assessment of the full range of each patient's medicine irrespective of therapy area. From its complaint, GlaxoSmithKline clearly believed that Chiesi's service was therapy area specific and the reviews were only focused on the medicines in the chosen therapy area. The therapy area determined by the GP was used to identify the cohort of patients who would be clinically assessed. The CSS pharmacist would then carry out a comprehensive therapeutic review of all the medicines for each patient irrespective of therapy area, as detailed above. This was why only pharmacists delivered the CSS therapeutic review service as they were the experts on medicines and the only health professional specifically qualified to provide a full therapeutic review across the patient's entire range of medicines. A complete review of a patient's full range of medicine enhanced patient care and benefitted the NHS; it improved the management of the patient's medical condition, improved health outcomes through optimal medicines use and reduced unwanted or unused medicines and thus reduced prescribing costs.

A clinical assessment by Chiesi's pharmacists did not always result in a change of the patient's medicine for a range of different clinical reasons and as outlined above, any clinical queries or recommendations which emanated or resulted from these assessments, were detailed on a medicine query form and discussed and resolved at the end of each working day directly with the authorising GP. Over the last two years no medicines had been changed in 45% of clinical assessments of patients by Chiesi's pharmacists.

Chiesi believed the service delivered by its pharmacists was a genuine therapeutic review which complied with the Code.

Chiesi noted that GlaxoSmithKline considered that

the service did not offer a comprehensive range of relevant treatment choices but was limited by the prescribing instructions given to practices by the local primary care pharmacy services.

Chiesi explained that the email was a confidential internal email from local health board to its practices stating its formulary choices, and Chiesi had neither input, nor any prior knowledge of its existence until it received a confidential copy from the local health board after it had been issued. Clearly Chiesi could not be held responsible for the contents of a third party document to which it had no input nor any prior knowledge of its content before circulation.

This email referred to specific Chiesi products; however Chiesi's CSS operated independently to any such specific local guidance. As detailed in Chiesi's CSS SOP, where the CSS was provided, then during the initial meeting between the GP and the CSS pharmacist, the GPs decided which therapy areas he/she would like reviewed and determined the medicines to be considered based on the comprehensive range of medicines which was available on the local formulary. The decisions regarding the therapy areas and range of medicines were those of the GPs themselves. The CSS pharmacist did not suggest to the GP which medicines should be considered. The GP could authorise any medicine(s) of their choice irrespective of any guidance from the local primary care organisation (PCO), such as provided in the email.

Chiesi believed its CSS offered a comprehensive range of relevant treatment choices and was not limited by the prescribing instructions given to practices by the local health board, in this instance, or any other such local prescribing guidelines. Each individual therapeutic review was determined by the authorizing GP at the outset. The service was not product specific and was not restricted to Chiesi's products.

Chiesi noted that GlaxoSmithKline considered that the clinical assessments carried out by the pharmacists were inadequate to ensure patient care was enhanced or maintained. In that regard Chiesi referred to the comprehensive clinical assessments outlined above.

In addition, in response to GlaxoSmithKline's concerns regarding a note-based review carried out by Chiesi's CSS, Chiesi clarified that its pharmacists could do either full patient-facing clinic reviews or note-based medicine reviews; SOPs existed for both types of review. As outlined above the GP controlled the review service and determined which type of review they required. Clearly in this case the GP required a note-based therapeutic review and this was performed as per the SOP provided. Chiesi's CSS offered both types of review and Chiesi acknowledged the benefits and the limitations each one could offer which was why the choice of review method was determined by the GP.

A note-based therapeutic review of the entire range of a patient's medicine with full access to the patient's medical history could deliver all the benefits already listed above, as the pharmacist could review all medicines in the context of the patient's medical condition, history and treatment. The main shortcoming of such a review was that the patient's treatment or dose might be changed without their direct involvement. For this reason an appropriate method of communicating any such changes was always agreed by the pharmacist with the GP and the patient was always given the opportunity to raise questions with the surgery. As well as raising any medicine queries directly with the GP at the end of each day, the pharmacist was also able to point out to the GP those patients they considered required a face-to-face consultation before any therapy change was made. Chiesi believed that such a review was in the interest of the patient as it was what their GP had determined was best for them, it benefitted the NHS and clearly a full review of the patient's medicine, even without the patient present, maintained and improved patient care in line with the Code.

A face-to-face review of the patient's medicine and condition allowed Chiesi's pharmacists to involve the patient as a full partner. Chiesi's pharmacists would listen to the patient's views about their medicines and take into account their preferences in any decisions about their treatment. A face-to-face review might be seen as the ideal as it provided an opportunity for a full concordant discussion about the patient's medicines, observations and counseling about the use of their medicines, such as inhaler technique, and recording of clinical measurements such as peak flow readings. A face-to-face review might be more likely to result in genuine agreement between the pharmacist and the patient, with the patient more likely to take their medicines as prescribed. However face-to-face medicine reviews did not always lead to a concordant discussion and they were more resource-intensive than a note-based review. In addition the GP might consider the previous surgery history of non-attendees at face-to-face clinics. A note-based review by a suitably qualified health professional's such as Chiesi's pharmacists might be preferable to no review which might be the outcome if only face-to-face clinics were adopted. All these were factors the GP might consider before finally choosing between a note-based or face-to-face review. Chiesi believed that both types of review enhanced and maintained patient care for the reasons outlined above and complied with the Code.

The Chiesi CSS was a non-promotional and non-product specific service. The team belonged to a non-promotional arm of the organization and was clearly de-lineated from the commercial part of the organization. The company also maintained a clear and distinct separation between the sales and service teams at all times and this was clearly defined with all Chiesi's SOPs. All members of the clinical support team were employees of Chiesi or external contractors employed by Chiesi to provide

the service operating under the management and SOPs of Chiesi. All members of the team who carried out therapeutic reviews were registered pharmacists and they reported into a director who was also a registered pharmacist. Before they carried out any therapeutic reviews the pharmacists were fully trained, and validated by the medical department, in the therapy areas and SOPs in which they would be working.

Chiesi's medical representatives were not involved in the therapeutic review process, except to sometimes, as a courtesy, to briefly introduce the clinical support pharmacist to the GP. The representative would then immediately leave the GP premises and would not return that day, or whilst the pharmacist was working within the practice. Any potential breach of the clear and distinct separation of sales and service by any member of staff, at any time, was considered a disciplinary offence as it would put the company in potential breach of the Code, and appropriate action was always taken by Chiesi's human resources department. If a representative received a request for a therapeutic review from a GP, he/she would refer the request to the clinical support office as outlined in their SOP.

Chiesi's CSS pharmacists were not bonused on sales, nor were they set targets based on patient numbers or product outcomes. This was a professional service provided by the company to deliver improved quality of care for patients and benefits to the NHS both of which enhanced the professional reputation of Chiesi with its customers.

Chiesi stated that all the documents provided which related to the CSS were strictly confidential as they would be of significant value and interest to third parties. Chiesi therefore requested that these were not disclosed to GlaxoSmithKline or any other party outside the PMCPA.

The Fostair SPC was provided and in the light of certain comments made by GlaxoSmithKline, Chiesi noted Section 4.1, Therapeutic indications:

Fostair is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting beta2-agonist) is appropriate.
- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonist or
- patients already adequately controlled on both inhaled corticosteroids and long acting beta2-agonists.

Note: Fostair is not appropriate for treatment of acute asthma attacks.

In summary, Chiesi submitted that its CSS was a professional service delivered by registered pharmacists who were the recognised experts on medicines and the health professionals' best positioned to carry out full therapeutic reviews across a patient's full range of medicines. As such the Clinical Support Therapeutic Review Service was in the interests of the patients, delivered benefits to the NHS and enhanced patient care in line with the requirements of their GPs.

Chiesi was disappointed that GlaxoSmithKline did not recognise pharmacists as the health professionals who were the experts on medicines or consider that pharmacists were qualified to carry out clinical assessments as described, which put the company at odds with the NHS and fellow members of the ABPI.

Chiesi's CSS delivered a quality therapeutic review service, not a switch programme. The therapeutic review service maintained high professional standards at all times, it enhanced patient care and it enhanced the reputation of both Chiesi and the rest of the pharmaceutical industry. Chiesi believed this service complied with all aspects of the Code and it strongly refuted GlaxoSmithKline's allegations of breaches of Clauses 18.4, 9.1 and 2.

FURTHER RESPONSES

In response to a request for further information Chiesi stated that it had received a copy of the email on 26 April 2010. In response, Chiesi CSS emailed the local health board on the same day stating 'Thank you for the email. We will now start contacting practices to arrange appropriate appointments and will keep you updated in the usual manner'. As this email was received by the CSS Chiesi did not tell its sales representatives about it. A copy of the email and response from Chiesi was sent to the local clinical support pharmacist only.

In response to a question about how Chiesi understood the service would be introduced by the health board to its practices the company stated that, as outlined in the email from the local health board, the CSS had assisted the local NHS, under an arrangement akin to a joint working partnership, for a number of years and had completed several successful projects. For the patients the projects had resulted in better care and a better experience of the healthcare system. For the NHS the projects had resulted in better use of resources, greater value for money and lower costs and Chiesi had been able to assist the local NHS with faster implementation of policies which were relevant to the company's business. This was essentially in line with the ABPI guidance notes on joint working between pharmaceutical companies and the NHS and others for the benefit of patients (taking into consideration the 2008 ABPI Code of Practice for the pharmaceutical industry) produced in March 2009.

Previously, communication of the CSS by the health board to its practices had been by email and the CSS had then those practices directly to arrange appointments for Chiesi pharmacists to offer the service in line with Chiesi SOPs. From the dialogue between the CSS and the local health board, Chiesi expected the service would be introduced by the health board to its practices in the same manner.

Chiesi clarified that the local health board email was not sent to Chiesi for comment or approval before it was issued. The company had no input nor any prior knowledge of the email's existence until it received the confidential copy from the local health board on 26 April.

In response to a further request for information about what Chiesi understood the health board would tell practices about the service, Chiesi reproduced in full its comment above about joint working practices and previous email communication. In addition Chiesi stated that it also understood that the health board would advise its practices that they might use the CSS to undertake therapeutic reviews to assist them implement the local NHS clinical priorities or in any therapy areas which they believed would benefit patient care in their respective practices. Chiesi also understood that individual prescribers at these practices would decide whether to use the CSS and that the health board could not make the individual prescribers or practices use the CSS.

PANEL RULING

The Panel noted Chiesi's submission that the CSS had assisted the local NHS, under an arrangement akin to a joint working partnership, for a number of years. Chiesi had referred to the ABPI guidance notes on joint working between pharmaceutical companies and the NHS. In the Panel's view the CSS was service provision, not joint working. Joint working covered situations where, for the benefit of patients, the NHS and one or more pharmaceutical companies pooled skills, experience and/or resources with a shared commitment to successful delivery of patient centered projects. Each party had to make a significant contribution and outcomes had to be measured. Treatments must be in line with nationally accepted clinical guidance where such existed and the arrangements between the parties must be open and transparent.

The Panel noted that Clause 18.4 permitted the provision of medical and educational goods and services which enhanced patient care, or benefitted the NHS and maintained patient care. The supplementary information to Clause 18.4, Switch and Therapy Review Programmes, explained that Clauses 18.1 and 18.4 prohibited switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine was simply changed to another without any clinical assessment. Companies could promote a simple switch from one product to another but not assist in its implementation. A therapeutic review which aimed to ensure that patients received optimal treatment following clinical assessment was a legitimate activity for a pharmaceutical company to support or assist. The decision to change or commence treatment must be made for each individual patient by the prescriber and every decision to change an individual patient's treatment must be documented with evidence that it was made on rational grounds. The Panel noted that GlaxoSmithKline had alleged that the current service, a review based on patients' medical records, was insufficient to enhance patient care or benefit the NHS and maintain patient care.

The Clinical Support Service Protocol (CHCS520100215), dated April 2010, explained that the service would enable PCOs and individual practices to carry out clinical assessments and therapeutic reviews of specific patient groups. The service was non promotional and non product specific. The GP retained full control of the process at all times.

The SOP Procedure for Asthma Therapeutic Review (CL002) dated 4 August 2010, began by referring to asthma control and the BTS/SIGN guidelines 2008. The introduction stated that when deemed necessary, an asthma clinic could be used to optimise patients' asthma control and provide reinforcement and education on the importance and achievability of good asthma control and hence improve quality of life. Section 2 stated that the CSS pharmacist would clarify with the GP whether the review was conducted with or without the patient. Factors which determined this included whether after clinical assessment any potential changes to a patient's asthma treatment might result in a change of molecule or device but would ultimately be determined by the GP's instructions. If the GP chose a paper review the Asthma Therapeutic Review Authorization Form (Non-Clinic) (CHCSS20100304 – June 2010) would be completed and identify: which patient groups should be reviewed; what the GP's treatments of choice were; which strengths should be used and any special instructions. The form stated that patients would be reviewed in accordance with BTS and National Institute for health and Clinical Excellence (NICE) Guidelines. Products were listed beneath the following headings: short-acting beta2 agonists, long acting beta2 agonists, inhaled corticosteroids, fixed inhaled corticosteroids/long-acting beta-agonist (ICS/LABA) combinations and others.

The Therapeutic Review Project Specification Form (CHCSS20100129) set out the services to be provided to the GP practice and the terms of service of a patient record review. It was noted that the result of a clinical assessment might require a face-to-face clinical assessment, possible changes in treatment including changes of dose, medicine or cessation of treatment. No medicines would be changed unless authorized by the GP or if, in the clinical judgement of the pharmacist, there was a query which required resolution or discussion by or with the GP. The GP and pharmacist would meet at the end of each working day and at the end of the review so, *inter alia*, the GP could summarize the completed work and authorize any further actions required. The authorizing GP was asked to sign each page of the patient lists to indicate that they were 'fully happy' with the action taken.

The SOP Procedure for Asthma Therapeutic Review (CL002) detailed how to conduct the search on a practice computer. A clinical rationale for any medicine change should be recorded. At the end of

the day the SOP mandated a further meeting with the GP to appraise them of the work carried out, sign off any treatment changes made and to address any queries. The SOP was supported by a training document SOP for pharmacists (CHCSS20100416 – August 2010) which stated that it would be usual to see the patients in a clinic setting unless the GP stipulated otherwise. The Clinical/Medication Query Form recorded any patient specific queries to be discussed with the GP.

The Panel noted that GlaxoSmithKline had provided a patient letter dated 5 October 2009 to support its allegations about the current service. The Panel noted that the SOP contemporaneous to the patient letter appeared to describe a different service, it was dated 2 April 2009 and bore the reference CL001. It described a review based on clinical assessment of a patient's records alone. There was no reference to a patient clinic. The GP authorized each step. The Panel did not have all the documentation for this review but considered that GlaxoSmithKline had not made specific allegations about it. In the Panel's view, the only issue to consider was whether a medical record review was adequate to, *inter alia*, enhance or maintain patient care.

The Panel noted that Thomas *et al* was a 2 year retrospective matched cohort study which evaluated the impact on asthma control of inhaler device switching without an accompanying consultation in general practice and determined that such a switch was associated with worsening asthma control. Doyle *et al* undertook qualitative interviews with 19 asthma patients who had experienced a non-consented switch of their inhaler device and concluded that such switches may, *inter alia*, diminish self-control associated with good asthma management. The Panel noted that there was some evidence in relation to changing a patient's device without consent. No clinical evidence had been submitted in relation to other changes such as a change in molecule, dose, etc. The Panel noted, however, that the CSS, based on patients' records, could potentially involve a change of device.

The Panel noted GlaxoSmithKline further considered that a *bona fide* therapeutic review should be closely aligned to BTS/SIGN best practice guidelines. As an example GlaxoSmithKline noted that moderately severe asthmatics on Seretide 125 were already at step 3 (of 5) of the BTS guidelines and required careful clinical assessment. The guidelines referred to access to primary care services delivered by doctors and nurses with appropriate training in asthma management and GlaxoSmithKline alleged that the use of pharmacists was at odds with this recommendation as was any written action plan. The Panel noted the BTS/SIGN guidelines and reference to clinical review by a nurse or doctor. The Panel noted that the guidelines were referred to in the introduction to the current SOP. The Panel did not consider that a medical record review by a pharmacist as part of the CSS meant that ongoing clinical care from a nurse or doctor was in any way precluded as implied by GlaxoSmithKline.

The Panel noted the SOP training document for pharmacists. The decision to have a medical notes review or clinic was taken by the authorizing GP. The SOP Procedure for Asthma Therapeutic Review and the SOP Training Document for Pharmacists made it clear that in some circumstances a clinic review might be preferable.

The authorizing GP defined the scope of the review, identified appropriate patients and had the final word on all matters in relation to it including product changes. In such circumstances the Panel did not consider that on the information before it about the current service a review of patients' records by a pharmacist in principle failed to enhance patient care or benefit the NHS and maintain patient care as alleged. No breach of Clauses 9.1 and 18.4 were ruled. The Panel consequently ruled no breach of Clause 2.

The Panel noted the requirements of Clause 18.4 and its supplementary information. A genuine therapeutic review should include a comprehensive range of relevant treatment choices, including non medicinal choices and should not be limited to the medicines of the sponsoring pharmaceutical company. The Panel noted that the email from the local NHS primary care pharmacy services encouraged practices to take up the assistance of the CSS to complete the three tasks outlined in the email. The first task was to review patients using CFC containing beclometasone inhalers and transfer them to CFC-free inhalers. The local formulary options were listed – Clenil modulite or Qvar for adults over 12 and Clenil Modulite for children. The second review was of Seretide 125 MDI patients with a possibility of transfer to Fostair MDI which was described as a local formulary option and a cost effective alternative to Seretide 125 MDI. The final option described assistance to optimize the prescribing of tramadol to the formulary preferred option of Maxitram SR.

The Panel noted that the copy of the email provided in Chiesi's response was the second page of a two page email which bore the date, beneath the text, of 28 April. Chiesi submitted that it received the email on 26 April. This discrepancy was explained in intercompany dialogue. Chiesi had not supplied a version of the email that it had received. It appeared that the only meaningful difference between the two versions was the date.

The Panel accepted, in general, that when *bona fide* therapeutic reviews were offered to practices the prescriber would, nonetheless, be aware which products were on the local formulary and he/she may decide, as a result of the review, that such products were suitable therapeutic options. However, in the view of the Panel, the content of the service and way it was offered must comply with the Code. Irrespective of what products were on the local formulary the review must offer the prescriber a comprehensive range of treatment choices. Pharmaceutical company assistance in the implementation of a switch service was unacceptable.

In the view of the Panel the email to practices from the local primary care pharmacy services was such that the prescriber's choice was, in effect, restricted to switching to those products mentioned therein. Practices would attach the greatest weight to the email. It was entirely unclear from Chiesi's responses what it knew about how the service would be introduced to local practices at the outset by the local health board other than such instruction would be by email. The Panel considered that on receipt of a copy of the email Chiesi knew that the local primary care pharmacy services was encouraging GPs to use its CS service in a way that rendered its provision in breach of the Code. That the email was sent independently and that Chiesi submitted that it had no prior knowledge of its content before it received a confidential copy was irrelevant. Once Chiesi knew about the email then it also knew that GPs were being encouraged to use the CS service to effect a switch programme. This was compounded by the wholly unacceptable provision by Chiesi of the email and the company's response to the local CSS pharmacist. The Panel had not seen the covering email provided to the local CSS pharmacist. Nonetheless it appeared that the local CSS pharmacist might have in effect been instructed to implement a switch service. Overall, the Panel considered that the arrangements did not meet the requirements of Clause 18.4 and a breach of that clause was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel considered that the provision of a switch service brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

APPEAL BY CHIESI

Chiesi submitted its CSS was in line with its comprehensive SOPs, training documents and associated approved CSS documents and was not a switch programme nor a switch service as ruled by the Panel. The SOPs were robust and independent of any third party recommendations. The CSS pharmacists were professional experts on medicines and the only health professional specifically qualified to provide a full therapeutic review across the patient's entire range of medicines. As registered pharmacists they had to comply with their own professional Code of Ethics which ensured the highest standards were always maintained. Chiesi appealed the ruling of a breach of Clause 9.1. The clinical assessments performed by the CSS pharmacists were thorough, offered a comprehensive range of relevant treatment choices and the provision of the service should not be judged on the contents of a third party email in isolation. The service provided transparent benefits to patients and the NHS. Chiesi submitted that the provision of its CSS in the local NHS, irrespective of the contents of the third party email, complied with Clause 18.4 and its supplementary information.

Chiesi submitted that its pharmacists took great pride in delivering enhanced quality of care to patients and the NHS. Regular positive feedback from GPs indicated their appreciation of the service and highlighted how it had delivered improved quality of care for their patients. This enhanced the reputations of Chiesi and the pharmaceutical industry. The CSS delivered in the local NHS was provided in a professional manner which reflected very positively on the industry and Chiesi did not believe, irrespective of any other ruling, that the service had brought discredit upon, or reduced confidence in, the pharmaceutical industry. Chiesi appealed the ruling of a breach of Clause 2.

Chiesi confirmed that it had received a copy of the email from the local NHS primary care pharmacy services on 26 April and that the contents were the same as provided by GlaxoSmithKline. The only dispute regarding this email was the inclusion of the date of '28th April' and the reference 'page 2 of 2', and this matter was clarified during inter-company correspondence. Chiesi had never disputed the contents as written by the local NHS primary care pharmacy services. Chiesi noted the Panel's concern that it did not provide a copy of the email it received on 26 April, however Chiesi was bound by the local NHS confidentiality and disclaimer notice attached to its copy and the Panel already had the full contents of the undisputed email from GlaxoSmithKline.

Chiesi noted the Panel's comment that it 'had not seen the covering email provided to the local CSS pharmacist. Nonetheless it appeared the local CSS pharmacist might have in effect been instructed to implement a switch service'. Chiesi submitted that the local CSS pharmacist was only copied on its email response of 26 April to the local NHS and this contained the original local NHS email as outlined in its response above. There was no covering email provided to the local CSS pharmacist and there were no instructions given to the local CSS pharmacist to implement a switch service.

Chiesi submitted that its CSS pharmacists were trained to comply with the SOPs and training documents submitted previously. A CSS pharmacist would never be instructed to implement a switch service as was alleged in the Panel ruling.

Chiesi noted the Panel's view that 'the email to practices from the local primary care pharmacy services was such that the prescribers' choice was, in effect, restricted to switching to those products mentioned therein. Practices would attach the greatest weight to the email'. Chiesi submitted that the email from the local NHS was sent directly to practice managers and not to GPs/prescribers. If the prescribing GP had not seen the email then his prescribing choice could not be restricted in the manner suggested. If the GP had seen the email, then as a self employed contractor to the NHS, and not an employee of the Health board, he would not be obliged to follow the guidance provided therein. Within primary care GPs had responsibility to improve patients' quality of care, expand the range of service to patients and to improve the working conditions for staff. GPs were responsible for prescribing as they considered appropriate for each patient. The health board might issue prescribing

guidance, such as in the email, but GPs were not obliged or contracted to follow such guidance and were free to make the prescribing decisions appropriate for each patient. Within the CSS the authorising GP, not the health board, determined any medicine changes. The Therapeutic Review Authorization forms which must be completed by GPs were blank and the GPs must determine their own treatment of choice in their own handwriting. GPs had absolute freedom to authorize any medicine(s) of their choice irrespective of any guidance from their health board and therefore the service allowed GP's a comprehensive range of treatment choices.

Chiesi submitted that the Panel's comment that 'Practices would attach the greatest weight to the email' was unsubstantiated, did not reference the prescriber or acknowledge the GPs' independence to prescribe. The CSS was delivered independently to any weight which might have been attached to the email by the practice, and allowed GPs a comprehensive range of treatment choices.

Chiesi noted that in its ruling the Panel 'considered that on receipt of the copy of the email Chiesi knew the local primary care pharmacy services was encouraging GPs to use its CS service in a way that rendered its provision in breach of the Code. That the email was sent independently and that Chiesi submitted that it had no prior knowledge of its content before it received a confidential copy was irrelevant. Once Chiesi knew about the email then it also knew that GPs were being encouraged to use the CS service to effect a switch programme'. Chiesi fully acknowledged the statement in the Panel's ruling that it operated the CSS in the full knowledge of the contents of the local NHS email as it believed the CSS delivered a genuine therapeutic review service provided in compliance with Clause 18.4.

As stated above, the local NHS email was sent to practice managers and so did not encourage GPs to use the CSS in a way that rendered its provision in breach of the Code, as it was not sent to them. The CSS was only authorized by GPs and not practice managers.

Chiesi noted that the Panel appeared to have ruled that the CSS provided a switch service based upon the contents of the third party email alone and not based upon how the CSS was actually delivered. The Panel did not refer to any of the comprehensive SOPs, training documents or any of the detailed explanation of the service provided in Chiesi's response. The CSS was always delivered in compliance with the SOPs and complied with all aspects of the Code. The service was not delivered nor amended to meet the stipulations of any third party email as had been ruled. For each of the three services outlined by the local NHS in its email, Chiesi submitted that it fully outlined below why it believed that the CSS provided complied with aspects of Clause 18.4 and its supplementary information.

Chiesi noted the three service reviews outlined in the local NHS email.

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

Chiesi submitted that the three therapeutic reviews were delivered by the CSS pharmacist who used the relevant SOP. The GP had to complete the relevant therapeutic review authorization form which was blank to allow him to state his treatments of choice in all classes of therapy irrespective of the guidance provided by the health board in the email. No medicine was simply changed to another without a clinical assessment.

The CSS pharmacist made a clinical assessment of each individual medicine of each individual patient in the patient cohort specified by the GP. This assessment was not limited to beclometasone or salmeterol/fluticasone medicines or tramadol modified release (according to the review being undertaken) but included a clinical assessment of each medicine currently prescribed for that patient. The CSS pharmacist assessed and recorded the following general points for discussion with the GP at the end of the day:

- interactions
- over/under ordering
- duplicate therapy
- compliance
- dosage
- strength
- licensed indication
- item on repeat not issued for 12 months
- quantities issued
- clinical investigation – tests overdue or results not recorded
- inequivalence of quantities eg 28 and 30 days supplies on same prescription
- side effects
- strength optimisation.

Chiesi submitted that a therapeutic review was different to a switch service. A therapeutic review service, which aimed to ensure that patients received optimal treatment following a clinical assessment, was a legitimate activity for a pharmaceutical company to support and/or assist. The CSS provided a therapeutic review service and not a switch service as ruled. This service ensured each patient received optimal treatment following the clinical assessment of each medicine they were prescribed. Chiesi submitted that this was a legitimate activity for it to support.

Chiesi submitted that the results of such clinical assessments might require, *inter alia*, changes of dose or medicine or cessation of treatment. A genuine therapeutic review should include a comprehensive range of relevant treatment choices, including non-medicinal choices, for the health professional and should not be limited to the medicines of the sponsoring pharmaceutical company. The results of the clinical assessments of each individual medicine of each individual patient within the therapeutic reviews might have included a number of outcomes. Chiesi gave comprehensive details of some of the changes in medicine which might have occurred. Some of the possible changes involved the prescription of other companies' medicines.

Chiesi submitted that as a result of these clinical assessments its CSS delivered a genuine therapeutic review which included a comprehensive range of relevant treatment choices, including non-medical choices, for the GP and these were not limited to Chiesi's products. Chiesi noted that in order to maintain patients on CFC-containing beclometasone on the same device, the only two CFC-free treatments available were Clenil Modulite (Chiesi) and Qvar (Teva), as outlined in the email.

Chiesi noted that the arrangements for a therapeutic review must enhance patient care, or benefit the NHS and maintain patient care, and must otherwise be in accordance with Clause 18.4 and the supplementary information on the provision of medical and educational goods and services.

Chiesi submitted that with regard to the second of the three services outlined in the local NHS email, a computer-based therapeutic review of the entire range of a patient's medicines with full access to the patient's medical history delivered all the benefits already listed above, as the pharmacist reviewed all medicines in the context of the patient's medical condition, history and treatment. During a computer-based therapeutic review, the patient's treatment or dose was changed without their direct involvement. For this reason an appropriate method of communicating for all changes was agreed by the CSS pharmacist with the GP and the patient was always able to raise questions with the surgery. As well as raising any medicine queries directly with the GP at the end of each day, the pharmacist was also able to bring to the attention of the GP any patients they considered required a face-to-face consultation before changes were made. As acknowledged by the Panel in its ruling, 'The authorising GP defined the scope of the review, identified appropriate patients and had the final word on all matters in relation to it including product changes'. Chiesi further submitted that a face-to-face clinic review of the patient's medicine and condition allowed the CSS pharmacist to involve the patient as a full partner, provided an opportunity for a full concordant discussion about the patient's medicines, allowed for observations and counselling about the use of their medicines, such as inhaler technique, and allowed clinical measurements such as peak flow to be recorded.

Either type of review, computer based or face-to-face, was in the patient's interest as it was what their GP had determined was best for them, benefitted the NHS and maintained and improved patient care in compliance with Clause 18.4.

Chiesi submitted that the full clinical assessment of each patient's individual medicine delivered by the CSS pharmacist as part of the therapeutic review service and as outlined above clearly enhanced patient care as it optimised their treatment and improved patient safety and adherence. In addition the clinical assessments provided by the CSS clearly benefitted the NHS for the reasons stated. The therapeutic review service was delivered in accordance with Clause 18.4 and the supplementary information on the provision of medical and educational goods and services as outlined.

Chiesi submitted that the decision to change or commence treatment must be made for each individual patient by the prescriber and every decision to change a patient's treatment must be documented with evidence that it was made on rational grounds.

Chiesi submitted that the CSS pharmacist carried out either a full patient-facing clinic review or computer-based therapeutic reviews as per the relevant SOP which stated:

'If any of the patient's asthma medication has been changed this should be recorded clearly on the patient cohort lists against the relevant name and a clinical rationale for the change must be annotated.'

'Once all patients have been clinically assessed, the CSS Pharmacist must meet again with the GP to go through the patient lists. He/she must sign each page of the patient lists to indicate that they are happy with the action taken and that it meets with their approval. Any queries noted on the Clinical/Medication Query Form must also be addressed and actioned according to the GP's wishes.'

Finally Chiesi noted the concerns raised by the Panel regarding the job description for the CSS pharmacists and the competencies required as defined within the job descriptions. Chiesi submitted that this was a non-promotional role and it would make the necessary representations to the Panel to explain how these competencies fitted within its own internal competency framework and the non-promotional role of the CSS pharmacist. This would be taken up with the Director of the PMCPA outside the scope of this appeal.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline agreed with the Panel that the activities carried out by and on behalf of Chiesi in the local area in late 2009 and early 2010 constituted the unacceptable practice of a company knowingly supporting an activity where patients would be screened and, on the basis of their receiving certain medicines, switched to one of a limited list of alternatives.

GlaxoSmithKline alleged that the two letters provided as part of its complaint clearly demonstrated Chiesi's support for:

1 A service which resulted in a letter informing a patient that their medicine was being switched from Seretide to Fostair. There did not appear to have been anything resembling a clinical assessment underlying this change and the patient was informed that the change of medicine was supported by Chiesi.

2 A service which provided assistance to primary care practices, covering three therapy areas where switching to alternative, Chiesi, medicines was advised. This service was described in a letter from the health board to a GP practice manager together with a summary of the medicines to be switched. The practice was asked to take advantage of the service offered by Chiesi.

GlaxoSmithKline alleged that irrespective of the intention of the service offered by Chiesi and the SOPs provided, Chiesi's provision of a therapy review service in the local area, where it knew that guidance would result in the identification of patients on certain medicines, with a view to switch them to alternatives supplied by Chiesi, was unacceptable. GlaxoSmithKline acknowledged that the guidance was provided by NHS staff and that the GP would retain final responsibility for prescribing choices. However, Chiesi failed in its responsibility to abide by the letter and spirit of the Code and by doing so, had breached the Code and misled health professionals as to what constituted good practice within the pharmaceutical industry.

GlaxoSmithKline stated that the SOPs provided by Chiesi (Asthma Therapeutic Review CHCSS20100515, August 2010 and Therapeutic review CHCSS20090280 Nov 2009) outlined a very robust process for the conduct of therapy reviews by the CSS pharmacists. GlaxoSmithKline assumed policies in place at the time of initiation of Chiesi's support were in line with the SOPs above.

GlaxoSmithKline stated that Chiesi cited these SOPs as evidence that the services provided in the local area did not breach the Code. However, GlaxoSmithKline's complaint did not relate to these documents. GlaxoSmithKline believed that implementing the services outlined within the SOPs with knowledge of and in support of the therapy switching objectives of the local NHS was clearly in breach of the Code.

As part of its appeal, Chiesi had also cited the professional responsibilities of pharmacists and GPs together with an argument that the advice was not issued directly to the GP as a reason why it was not in breach of Clauses 18.4, 9.1 and 2. GlaxoSmithKline alleged that citing the professional abilities and Code of Ethics of the Chiesi CSS pharmacists, or arguing that the guidance email from the local health board was sent to practice managers and not to GPs, who would be free to make their own treatment decisions rather than following the advice issued, was irrelevant and demonstrated that Chiesi did not understand its responsibilities and as such had acted in a way to damage its reputation and that of the industry in general.

Chiesi went on to state that even if GPs knew about the advice issued by the health board, they did not need to follow it. GlaxoSmithKline alleged that this further reflected Chiesi's lack of responsibility for its involvement in the switch service and also showed a lack of regard and/or insight into how the NHS operated.

GlaxoSmithKline was confident that the services outlined in the SOPs could be implemented by Chiesi in a way that benefitted patients and the NHS and complied with the Code. However, in this case, Chiesi had failed in its responsibility to ensure that its services were provided in a compliant way.

Despite Chiesi's reasons for appeal, GlaxoSmithKline continued to allege that in its provision of support in the local NHS, Chiesi had breached Clauses 18.4, 9.1 and 2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, stated that switch services paid for or facilitated directly or indirectly by a pharmaceutical company were prohibited. A therapy review service which aimed to ensure that patients received optimal treatment following a clinical assessment was a legitimate activity for a pharmaceutical company to support and/or assist. A genuine therapeutic review should include a comprehensive range of relevant treatment choices, including non medicinal choices and should not be limited to the medicines of the sponsoring pharmaceutical company.

The Appeal Board noted that the local NHS email informed the reader that they might be contacted by [Chiesi] and that the company could provide support to assist with a number of actions on prescribing which were relevant to the local NHS. In particular, practices were encouraged to take up the assistance of the CSS to complete the three tasks outlined. The first task was to review patients using CFC-containing beclometasone inhalers and transfer them to CFC-free inhalers. The local formulary options listed were Clenil Modulite or Qvar for adults and children over 12 and Clenil Modulite for children. The second review was of Seretide 125 MDI patients with a possibility of transfer to Fostair MDI which was described as a local formulary option and a cost effective alternative. The final task listed was to seek assistance to optimize the prescribing of tramadol modified release formulations to the formulary preferred option of Maxitram SR.

The Appeal Board noted that upon receipt of a copy of the email Chiesi responded by stating 'Thank you

for the email. We will now start contacting practices to arrange appropriate appointments and will keep you updated in the usual manner'. The Appeal Board was extremely concerned that Chiesi's response showed that the company intended to act proactively to assist in the implementation of the local NHS' prescribing plans as outlined in the email. A copy of the email and Chiesi's response was sent to the local CSS pharmacist and, in the Appeal Board's view, would inevitably influence his/her interactions with local practices.

The Appeal Board considered that the email from the local NHS was, in effect, advice from the local primary care organization that certain patients should be switched to certain Chiesi products. Such advice would be influential; in the Appeal Board's view prescribers would need good reasons not to follow it. The Appeal Board considered that Chiesi was naive to state that because the email was sent to practice managers and not to GPs the GPs would not be influenced by it; practice managers were bound to discuss the email with them. The Appeal Board considered that pharmaceutical company assistance in the implementation of the switch services detailed in the email was unacceptable.

Overall, the Appeal Board considered that Chiesi's role in supporting the implementation of the local NHS advice did not meet the requirements of Clause 18.4 and it upheld the Panel's ruling of a breach of that clause. High standards had not been maintained and the Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The Appeal Board considered that changing a patient's medicine was an extremely sensitive situation and the utmost care was needed. The provision of a switch service brought discredit upon, and reduced confidence in, the pharmaceutical industry and the Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on all points was unsuccessful.

Complaint received **20 August 2010**

Case completed **28 February 2011**

CASE AUTH/2362/10/10

BOEHRINGER INGELHEIM v NOVARTIS

Promotion of Onbrez

Boehringer Ingelheim complained about a leavepiece for Onbrez Breezhaler (indacterol inhalation powder) issued by Novartis. Onbrez was indicated for maintenance bronchodilator treatment of airflow obstruction in adults with chronic obstructive pulmonary disease (COPD). The recommended dose for inhalation was the content of one 150mcg capsule once a day; the inhalation of the content of one 300mcg capsule once a day had been shown to provide additional clinical benefit with regard to breathlessness, particularly in patients with severe COPD.

The detailed response from Novartis is given below.

Boehringer Ingelheim alleged that the term 'strength' in the claim 'Sustained strength that helps your patients with COPD meet the varied demands of daily life' was too generalised to substantiate. This was not a meaningful clinical indicator and did not help the prescriber judge when or how to use Onbrez.

The Panel noted that the front cover of the leavepiece was headed 'NEW Onbrez Breezhaler: the first 24 hour [long-acting beta$_2$-agonist] for COPD' and featured the picture of a lion apparently leaping, full stretch, from an inhaler device. The headline above the picture was 'Sustained strength that helps your patients with COPD meet the varied demands of daily life'. The Panel considered that the unqualified use of the word 'strength' was misleading; there was no indication as to what, in that context, 'strength' meant. The Panel noted Novartis' submission that 'strength' related to significant clinically meaningful efficacy in a given disease state and in that regard considered that 'strength' could be applied to all medicines. The Panel queried Novartis' submission that in the context of COPD health professionals would equate 'strength' with efficacy in terms of markers for lung function. The Panel considered that the strong, unqualified claim was misleading and, in that regard, could not be substantiated. The Panel also considered that the unqualified use of the word 'strength' implied some special property which could not be substantiated. Breaches of the Code were ruled. The Panel did not consider that the unqualified use of 'strength' was such that it did not help prescribers judge when or how to use Onbrez. No breach of the Code was ruled.

Boehringer Ingelheim alleged that in the strapline 'Sustained relief in COPD' which appeared below the Onbrez product logo, relief from what was not made clear.

The Panel noted that Onbrez was the first long-acting beta$_2$-agonist for COPD. Section 5.1 of the SPC stated that 'The 24-hour bronchodilator effect of Onbrez Breezhaler was maintained from the first dose throughout a one-year treatment period with no evidence of loss of efficacy'. The Panel noted that Onbrez was indicated for maintenance of bronchodilator treatment of airflow obstruction in adults with COPD. The Panel considered that shortness of breath would be a major presenting symptom of COPD. In that regard the Panel did not consider that the strapline 'Sustained relief in COPD' was misleading as alleged; the claim could be substantiated and did not exaggerate the medicine's properties. No breach of the Code was ruled.

Boehringer Ingelheim alleged that the use of an asterisked footnote to qualify the claim 'Rapid bronchodilation* within 5 minutes that lasts all day' was not adequate. The asterisk referred to the footnote 'Onbrez Breezhaler is not licensed for acute symptomatic relief'.

The Panel noted that the claim was referenced to Vogelmeier *et al* (2009) (INTIME study) and Feldman et al (2009) (INLIGHT– 1 study). Novartis had submitted that the INSURE study (Balint *et al* 2009) also supported the claim for a rapid onset of action. The INTIME study demonstrated that Onbrez had an onset of action within 5 minutes on the first day of dosing. The INLIGHT-1 study authors concluded, inter alia, that Onbrez demonstrated a fast onset (within 5 minutes) of bronchodilation from the first dose and the single dose INSURE study showed that Onbrez significantly increased FEV_1 at 5 minutes post-dose.

The Panel noted that Section 5.1 of the SPC stated that there was a rapid onset of action within 5 minutes after inhalation. It was not clear from the SPC whether this was demonstrated each day when Onbrez was used for long-term therapy.

The Panel noted that COPD was a chronic disease and, as such, patients would require long-term therapy. The Panel noted that studies had shown that rapid bronchodilation was observed with the first dose of Onbrez. Novartis had not submitted data to show that subsequent daily doses of Onbrez also produced rapid bronchodilation within 5 minutes. In any event the Panel questioned the relevance of promoting a short onset of action in a long-term therapy when that long-term therapy was not also indicated for acute use. The Panel considered that the claim was misleading and ruled a breach of the Code.

Boehringer Ingelheim noted the claim

'Improvements in breathlessness at least as effective as salmeterol and tiotropium'. Section 5.1 of the Onbrez SPC, 'Symptomatic benefits', stated, inter alia, that 'The magnitude of response was generally greater than seen with active comparators'. However there was a reference to table 2 of the SPC which included the percentage of patients who achieved the minimal clinically important difference TDI (transition dyspnoea index) – 57% for indacterol and 57% for tiotropium. 'At least as effective', implied possible superiority. Boehringer Ingelheim thus alleged that this was misleading and exaggerated.

Boehringer Ingelheim noted that no reference was made on the same page as the claim to the open label nature of the study design which was also necessary to understand the clinical data. This item did not provide enough information for the prescriber to make informed decisions regarding the clinical data.

The Panel noted that the claim 'Improvements in breathlessness at least as effective as salmeterol and tiotropium' was referenced to Kornmann *et al* (2009) (INLIGHT-2 study) and Donohue *et al* (2010) (INHANCE study). Kornmann *et al* did not show a clinically significant difference in terms of trough FEV_1 and the transition dyspnea index between indacterol and salmeterol. There was a statistically significant advantage for indacterol with regard to rescue-free days. Similarly, Donohue *et al* failed to show a clinically significant difference between indacterol and tiotropium in terms of trough FEV_1 and transition dyspnea index.

The Panel did not consider that the claim at issue reflected the balance of the evidence. The claim implied possible clinical superiority for indacterol whereas in terms of trough FEV_1 and the transition dyspnea index, it had only been shown to be clinically similar to salmeterol and tiotropium. The Panel considered that the claim was misleading as alleged. The Panel further considered that the claim was insufficiently complete such as to enable a prescriber to make an informed decision regarding the clinical data. Breaches of the Code were ruled.

Boehringer Ingelheim noted the claim 'Significantly more patients experienced clinically meaningful improvements in quality of life vs. other bronchodilators'.

There was no reference on the page to the open label nature of the study design which was necessary to understand the clinical data. The leavepiece did not provide enough information for the prescriber to make informed decisions regarding the clinical data.

The Panel noted that the claim was referenced to Kornmann *et al* (IN-LIGHT 2 study) and Yorgancioglu *et al* (2009) (INHANCE study). Kornmann *et al* compared indacterol and salmeterol and reported that indacterol-treated patients had an improved health status with a 2.1 unit difference over salmeterol ($p<0.05$) at week 12. This difference, however, although statistically significant was less than the minimum clinically important difference of 4 points. There was no difference between the two products at week 26.

Yorgancioglu *et al* compared indacterol 150mcg and 300mcg and tiotropium 18mg all given once daily. The tiotropium was administered under open-label conditions. In terms of the percentage of patients achieving a clinically important difference of ≥4 units vs placebo in a health related quality of life score, there was a statistically significant difference between tiotropium and both doses of indacterol at weeks 4 and 8 in favour of indacterol; there was no difference between the medicines at week 12 and at week 26 there was only a statistically significant advantage for the lower dose of indacterol vs tiotropium.

The Panel considered that the claim at issue did not provide enough information about the clinical data as alleged. The Panel did not accept that the fact that another page of the leavepiece stated that the tiotropium study was open-label was sufficient as submitted by Novartis. A breach of the Code was ruled.

Boehringer Ingelheim noted that the claim 'Onbrez Breezhaler: improvements in quality of life in more patients than salmeterol or tiotropium' appeared as the headline on a page which featured a bar chart depicting the results of Yorgancioglu *et al*. The claim was referenced to Kornmann *et al* and Yorgancioglu *et al*.

Boehringer Ingelheim alleged that Novartis had cherry-picked the data to report the improvements in quality of life (QoL) vs tiotropium at 26 weeks. Whilst there were differences in QoL between the indacterol and the tiotropium groups these were small and inconsistent. At weeks 4, 8 and 26 there was a significant improvement in the indacterol group compared with the tiotropium group. However, at 12 weeks there was no significant difference in QoL between the groups.

The Panel noted that Kornmann *et al* reported that at week 12 the percentage of patients who achieved a clinically important improvement in a quality of life score was highest in the indacterol group (57.9%) compared with salmeterol (46.8%) and placebo (39.1%) groups.

The claim headed a page which featured a bar chart which depicted the results at 26 weeks of Yorgancioglu *et al*. The bar chart showed that at week 26, 47.3% of patients treated with tiotropium had a clinically significant improvement in a quality of life measurement vs 57.8% in the indacterol 150mcg treated group ($p<0.01$). There was, however, no significant difference between the percentage of patients achieving a clinically important improvement in the indacterol 300mcg treated group (52.5%) vs the tiotropium group (47.3%).

Yorgancioglu *et al* had shown that at weeks 4, 8 and 26, a statistically significantly greater percentage of patients on indacterol 150mcg achieved a clinically important difference in quality of life vs tiotropium-treated patients (p<0.01). Only at week 12 was there no statistically significant difference between the two treatment groups. Thus, in three out of the four time points measured there had been a statistically significant advantage for indacterol 150mcg vs tiotropium. The Panel further noted Novartis' submission that tiotropium reached its maximal effect in 6 months as evidenced by a peak in FEV_1. The Panel did not consider that to show the 26 week data was 'cherry picking' as alleged. No breach of the Code was ruled.

Boehringer Ingelheim alleged that five small drawings each showing a different step in the correct use of the Breezhaler device which were an abridged version of the instructions for use found in the patient information leaflet and the SPC, implied that the process for use was simpler than it actually was. This was misleading and could cause misunderstandings between patients and prescribers: prescribers might not appreciate that it was necessary to work through a 13 step process.

The Panel noted that the instructions for use had been given in an abbreviated form in the leavepiece; 5 steps had been illustrated compared with the 13 shown in the SPC. The Panel considered that although more instructions would have been helpful, the 5 steps shown were not misleading per se. No breach of the Code was ruled.

Boehringer Ingelheim Limited complained about a six page, gate-folded leavepiece (ref IND10-010) for Onbrez Breezhaler (indacterol inhalation powder) issued by Novartis Pharmaceuticals UK Ltd. Onbrez was indicated for maintenance bronchodilator treatment of airflow obstruction in adults with chronic obstructive pulmonary disease (COPD). The recommended dose for inhalation was the content of one 150mcg capsule once a day; the inhalation of the content of one 300mcg capsule once a day had been shown to provide additional clinical benefit with regard to breathlessness, particularly in patients with severe COPD. Onbrez was the first 24-hour long-acting $beta_2$-agonist (LABA) for COPD. Boehringer Ingelheim marketed Spiriva (tiotropium) which was indicated for the maintenance treatment of COPD. Spiriva was also a powder inhalation to be used once daily.

Inter-company dialogue had failed to resolve the issues.

1 Claim 'Sustained strength that helps your patients with COPD meet the varied demands of daily life'

This claim appeared as a headline on the front page (page 1) of the leavepiece.

COMPLAINT

Boehringer Ingelheim alleged that 'strength' was too generalised a claim to substantiate. This was not a meaningful clinical indicator and did not help the prescriber judge when or how to use Onbrez. Breaches of Clauses 7.2, 7.4 and 7.10 were alleged.

RESPONSE

Novartis submitted that it was clear to any health professional that in the context of COPD, 'strength' indicated significant efficacy in terms of markers for lung function such as forced expiratory volume in one second (FEV_1) and the associated relevant improvements in patient symptoms and quality of life. In a number of large, double-blind, placebo controlled studies (INLIGHT-1, INLIGHT-2, INVOLVE, INHANCE) indacterol had repeatedly and consistently demonstrated improvements in FEV_1 in COPD patients and associated relevant improvements in symptoms and quality of life of such magnitude and duration as to be clinically significant – justifying the use of 'strength'. Novartis noted that this did not claim or imply superiority over any other therapy – but rather, significant clinically meaningful efficacy in a given disease state. Further, the claim 'Sustained strength' was supported by the evidence cited in the summary of product characteristics (SPC) which showed that indacterol provided bronchodilation which lasted for 24 hours and that this effect was sustained over 1 year of treatment.

Novartis, therefore, denied breaches of Clauses 7.2, 7.4 and 7.10.

PANEL RULING

The Panel noted that the front cover of the leavepiece was headed 'NEW Onbrez Breezhaler: the first 24 hour LABA for COPD' and featured the picture of a lion apparently leaping, full stretch, from an inhaler device. The headline above the picture was 'Sustained strength that helps your patients with COPD meet the varied demands of daily life'. The Panel considered that the unqualified use of the word 'strength' was misleading; there was no indication as to what, in that context, 'strength' meant. The Panel noted Novartis' submission that 'strength' related to significant clinically meaningful efficacy in a given disease state and in that regard considered that 'strength' could be applied to all medicines. The Panel queried Novartis' submission that in the context of COPD health professionals would equate 'strength' with efficacy in terms of markers for lung function. The Panel considered that the strong, unqualified claim was misleading and, in that regard, could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. Further, the Panel considered that the unqualified use of the word 'strength' implied some special property which could not be substantiated. A breach of Clause 7.10 was ruled. The Panel did not consider that the unqualified use of 'strength' in the claim was such that it did not help prescribers judge when or how to

use Onbrez. No breach of Clause 7.2 was ruled.

2 Claim 'Sustained relief in COPD'

This claim appeared as the strapline below the Onbrez product logo on pages 1 and 6 of the leavepiece.

COMPLAINT

Boehringer Ingelheim submitted that relief from what was not made clear. Breaches of Clauses 7.2, 7.4 and 7.10 were alleged.

RESPONSE

Novartis submitted that in the context of COPD, it was clear to the health professional that 'sustained relief' was from symptoms. For patients with COPD, it was widely accepted that the most consistently troublesome symptom was shortness of breath. It was the primary symptom that had the greatest impact on patients' lives, limiting their exercise capacity and adversely affecting their quality of life. Indacterol had been shown to consistently provide COPD patients with sustained relief from breathlessness (as shown by improvements in the Transitional Dysponoea Index (TDI) scores and reduced need for rescue medication) and associated improvements in quality of life, which were statistically and clinically superior to placebo and sustained over 24 hours for the duration of therapy.

Novartis submitted that the strapline could be substantiated and supported by the clinical evidence. The company denied the alleged breaches of Clauses 7.2, 7.4 and 7.10.

PANEL RULING

The Panel noted that Onbrez was the first long-acting beta$_2$-agonist for COPD. Section 5.1 of the SPC stated that 'The 24-hour bronchodilator effect of Onbrez Breezhaler was maintained from the first dose throughout a one-year treatment period with no evidence of loss of efficacy'. The Panel noted that Onbrez was indicated for maintenance of bronchodilator treatment of airflow obstruction in adults with COPD. The Panel considered that shortness of breath, limiting exercise capacity and the ability to perform daily activities, would be a major presenting symptom of COPD. In that regard the Panel did not consider that the strapline 'Sustained relief in COPD' was misleading as alleged. No breach of Clause 7.2 was ruled. The Panel considered that the claim could be substantiated and did not exaggerate the medicine's properties. No breach of Clauses 7.4 and 7.10 were ruled.

3 Claim 'Rapid bronchodilation* within 5 minutes that lasts all day'

This claim appeared as the first in a list of five bullet points on the inside flap (page 5) of the leavepiece. The asterisk referred to a footnote which read 'Onbrez Breezhaler is not licensed for acute symptomatic relief'.

COMPLAINT

Boehringer Ingelheim alleged that the use of an asterisk and footnote to qualify the rapid 5 minute bronchodilation claim was not adequate and in breach of Clause 7.

RESPONSE

Novartis submitted that the claim 'Rapid bronchodilation within 5 minutes that lasts all day' was clearly supported by the statements in Section 5.1 of the Onbrez Breezhaler SPC which read 'There was a rapid onset of action within 5 minutes after inhalation …' and 'Onbrez Breezhaler, administered once a day at doses of 150 and 300 microgram consistently provided clinically significant improvements in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours across a number of clinical pharmacodynamic and efficacy studies'. In addition, this was further supported by the once daily dosing schedule.

Clinical data from the INSURE and INTIME studies demonstrated that indacterol had a rapid onset of action, and the INLIGHT-1 study, along with the active comparator trials, all demonstrated that indacterol had a 24-hour duration of action. The claim was, therefore, appropriate, could be referenced and did not require qualification.

The statement 'Onbrez Breezhaler is not licensed for acute symptomatic relief' was not included to qualify the claim but for completeness and to avoid doubt as the product was indicated for maintenance bronchodilator treatment of airflow obstruction in adults with COPD; it was not indicated as an acute treatment. The additional wording was not a claim or 'selling point' of the product. It was, therefore, inappropriate to consider this as a breach under Clause 7.

PANEL RULING

The Panel noted that the claim 'Rapid bronchodilation within 5 minutes that lasts all day' was asterisked to the footnote 'Onbrez Breezhaler is not licensed for acute symptomatic relief'. The Panel further noted that the claim itself was referenced to Vogelmeier *et al* (2009) (INTIME study) and Feldman *et al* (2009) (INLIGHT– 1 study). Novartis had submitted that the INSURE study (Balint *et al* 2009) also supported the claim for a rapid onset of action.

The Panel noted that Section 5.1 of the SPC stated that there was a rapid onset of action within 5 minutes after inhalation. It was not clear from the SPC whether this was demonstrated each day when Onbrez was used for long-term therapy.

The INTIME study demonstrated that Onbrez had an onset of action within 5 minutes on the first day of dosing. The INLIGHT-1 study measured trough FEV_1 ie between 23 and 24 hours post-dose after 12 weeks of treatment but also measured FEV_1 at individual time points on day 1. The study authors concluded, inter alia, that Onbrez demonstrated a fast onset (within 5 minutes) of bronchodilation from the first dose. The INSURE study was a single dose study which showed that Onbrez significantly increased FEV_1 at 5 minutes post-dose.

The Panel noted that COPD was a chronic disease and, as such, patients would require long-term therapy. The Panel noted that studies had shown that rapid bronchodilation was observed with the first dose of Onbrez. Novartis had not submitted data to show that subsequent daily doses of Onbrez also produced rapid bronchodilation within 5 minutes. In any event the Panel questioned the relevance of promoting a short onset of action in a long-term therapy when that long-term therapy was not also indicated for acute use. The Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

4 Claim 'Improvements in breathlessness at least as effective as salmeterol and tiotropium'

This claim appeared as the third in a list of five bullet points on the inside flap (page 5) of the leavepiece.

COMPLAINT

Boehringer Ingelheim noted that Section 5.1 of the Onbrez SPC, 'Symptomatic benefits', stated, inter alia, that 'The magnitude of response was generally greater than seen with active comparators'. However there was a reference to table 2 of the SPC which included the percentage of patients who achieved the minimal clinically important difference TDI (transition dyspnoea index) – 57% for indacterol and 57% for tiotropium. 'At least as effective', implied possible superiority (ref Case AUTH/2270/10/09). Boehringer Ingelheim thus alleged that this was misleading in breach of Clause 7.2 as it was an exaggeration.

Boehringer Ingelheim noted that no reference was made on this page of the leavepiece to the open label nature of the study design which was also necessary to understand the clinical data. This item did not provide enough information for the prescriber to make informed decisions regarding the clinical data. A breach of Clause 7.2 was alleged.

RESPONSE

Novartis stated that it had conducted a number of separate clinical studies relating to indacterol. The INHANCE study showed that 71% of patients receiving indacterol 300mcg and 62% of patients receiving indacterol 150mcg reached the minimal clinically important difference for TDI. The comparable figures for tiotropium and placebo were 57% and 47% respectively. The INLIGHT-2 study showed that 57% of patients given indacterol 150mcg, 54% of salmeterol patients and 45% of placebo patients reached the minimal clinically important difference for TDC. The INLIGHT-2 study did not compare indacterol with tiotropium. In order to compare indacterol 150mcg with tiotropium one would have to use the full data from the INHANCE study. Novartis noted that Boehringer Ingelheim had selected the tiotropium figure from the INHANCE study, but then used the indacterol 150mcg data from the INLIGHT-2 study where there was no tiotropium comparator arm. Novartis considered that this was an inappropriate and misleading comparison. With respect to 'at least as effective as', the INHANCE study demonstrated that indacterol 150mcg and 300mcg showed comparable efficacy to tiotropium, however, for some endpoints there were statistically significantly improvements for indacterol vs tiotropium. The statement 'at least as effective as' was therefore accurate and justifiable and Novartis denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim 'Improvements in breathlessness at least as effective as salmeterol and tiotropium' was referenced to Kornmann *et al* (2009) (INLIGHT-2 study) and Donohue *et al* (2010) (INHANCE study).

Kornmann *et al* compared the efficacy and safety of once-daily indacterol 150mcg (n=330) and twice-daily salmeterol 50mcg (n=333) in patients with moderate to severe COPD in a randomized, double-blind, placebo-controlled, parallel-group study. Trough FEV_1 at 12 weeks was 60ml higher with indacterol than salmeterol ($p<0.001$) and this statistically significant treatment difference was maintained at week 26. The Panel noted, however, that a 120ml difference had been preset as denoting a clinical difference. Although indacterol improved the week 12 transition dyspnea index by 0.55 over salmeterol ($p=0.015$), a difference of 1 was considered clinically important. Indacterol allowed significantly more rescue-free days over 26 weeks (60% vs 55% with salmeterol ($p<0.05$)). The authors concluded, inter alia, that once-daily indacterol was superior to twice-daily salmeterol in its 24 hour bronchodilator effect and improved other clinical outcomes more than salmeterol.

Donohue *et al* compared the efficacy of indacterol and tiotropium over 26 weeks. Patients with moderate to severe COPD were randomised to double-blind, once-daily indacterol 150mcg (n=416) or 300mcg (n=416) or tiotropium 18mcg once-daily (n=415). At week 12, trough FEV_1 was 40-50ml greater in the indacterol patients than the tiotropium patients and although statistically significant when tested for superiority and non-inferiority ($p\leq0.01$ and $p<0.001$ respectively) the difference was less than the prespecified minimum important clinical difference of 120ml. The effects of indacterol and tiotropium were maintained over the course of the study. With regard to the transition dyspnea index

the proportion of patients with a clinically important improvement from base line was statistically significantly greater in the indacterol 300mcg group compared to tiotropium patients at weeks 4, 8, 12 and 26. There was no statistically significant difference between the indacterol 150mcg group and the tiotropium group at any of these time points. With regard to the transition dyspnea index total score, a bar chart in Donohue *et al* showed that the difference between tiotropium and indacterol was in favour of indacterol but always less than the clinically important difference of 1.

Donohue *et al* noted that the design of the study might have favoured indacterol therapy given that the tiotropium arm was open whereas the indacterol arm was double-blind. Nonetheless the authors believed that the study strongly indicated that indacterol was at least as effective as tiotropium.

The Panel noted that Kornmann *et al* had not shown a clinically significant difference in terms of trough FEV_1 and the transition dyspnea index between indacterol and salmeterol. There was a statistically significant advantage for indacterol with regard to rescue-free days. Similarly, Donohue *et al* had failed to show a clinically significant difference between indacterol and tiotropium in terms of trough FEV_1 and transition dyspnea index.

The Panel did not consider that the claim at issue reflected the balance of the evidence. The claim implied possible clinical superiority for indacterol whereas in terms of trough FEV_1 and the transition dyspnea index, the medicine had only been shown to be clinically similar to salmeterol and tiotropium. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel further considered that the claim was insufficiently complete such as to enable a prescriber to make an informed decision regarding the clinical data. A further breach of Clause 7.2 was ruled.

5 Claim 'Significantly more patients experienced clinically meaningful improvements in quality of life vs. other bronchodilators'

This claim appeared as the fourth in a list of five bullet points on the inside flap (page 5) of the leavepiece.

COMPLAINT

Boehringer Ingelheim noted that page 5 did not refer to the open label nature of the study design which was necessary to understand the clinical data. The leavepiece did not provide enough information for the prescriber to make informed decisions regarding the clinical data in breach of Clause 7.2.

RESPONSE

Novartis submitted that the claims on page 5 summarized the key messages for Onbrez Breezhaler. It was clear from the graph on the opposite page (page 2) in the leavepiece illustrating the comparison of indacterol with tiotropium and placebo in the INHANCE study that the tiotropium arm of this study was, indeed, open-label. This was stated twice on page 2. Novartis therefore denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim on page 5 was referenced to Kornmann *et al* (IN-LIGHT 2 study) and Yorgancioglu *et al* (2009) (INHANCE study).

Kornmann *et al* compared indacterol and salmeterol and reported that indacterol-treated patients had an improved health status with a 2.1 unit difference over salmeterol ($p<0.05$) at week 12. This difference, however, although statistically significant was less than the minimum clinically important difference of 4 points. There was no difference between the two products at week 26.

Yorgancioglu *et al* compared indacterol 150mcg and 300mcg and tiotropium 18mg all given once daily. The tiotropium was administered under open-label conditions. In terms of the percentage of patients achieving a clinically important difference of ≥4 units vs placebo in a health related quality of life score, there was a statistically significant difference between tiotropium and both doses of indacterol at weeks 4 and 8 in favour of indacterol; there was no difference between the medicines at week 12 and at week 26 there was only a statistically significant advantage for the lower dose of indacterol vs tiotropium.

The Panel considered that the claim at issue did not provide enough information about the clinical data as alleged. The Panel did not accept that the fact that page 2 of the leavepiece stated that the tiotropium study was open-label was sufficient as submitted by Novartis. A breach of Clause 7.2 was ruled.

6 Claim 'Onbrez Breezhaler: improvements in quality of life in more patients than salmeterol or tiotropium'

This claim appeared as the headline on the inside front page (page 2) which featured a bar chart depicting the results of Yorgancioglu *et al*. The claim was referenced to Kornmann *et al* and Yorgancioglu *et al*.

COMPLAINT

Boehringer Ingelheim submitted that the quality of life (QoL) outcomes, as reported by the St Georges Respiratory Questionnaire (SGRQ), were reported as secondary outcome measures at weeks 4, 8, 12 and 26 in Yorgancioglu *et al*, published in poster form at the 2009 European Respiratory Society (ERS) meeting.

Boehringer Ingelheim noted that Novartis had reported the improvements in QoL vs tiotropium at 26 weeks. This was 'cherry-picking' the data. Whilst there were differences in QoL between the indacterol and the tiotropium groups these were small and inconsistent. At weeks 4, 8 and 26 there was a significant improvement in the indacterol group compared with the tiotropium group. However, at 12 weeks there was no significant difference in QoL between the groups. Boehringer Ingelheim alleged a breach of Clause 7.2.

RESPONSE

Novartis submitted that the data for tiotropium was presented at 6 months as this was when tiotropium had been shown to reach its maximal effect in COPD patients (as evidenced by the peak in FEV_1 at 6 months in the UPLIFT trial (Tashkin *et al* 2008). Novartis therefore considered that a comparison at 6 months was the fairer option and of greater relevance to clinicians. Although there was no significant difference between indacterol and tiotropium at week 12, a statistically significant difference was observed between these arms of the study at all other time points (weeks 4, 8 and 26). The fact that the results showed a difference in three out of four of the time points (2 before [at weeks 4 and 8] and 1 after the 12 week point [at week 26]) suggested that there was a good degree of consistency. It would indeed be 'cherry-picking' to suggest that the 12 week value (no difference) was the most representative time point of the study as Boehringer Ingelheim seemed to imply. Novartis denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim was referenced to Kornmann *et al* and Yorgancioglu *et al* as in point 5 above. Kornmann *et al* reported that at week 12 the percentage of patients who achieved a clinically important improvement in a quality of life score (≥4 units) was highest in the indacterol group (57.9%) compared with salmeterol (46.8%) and placebo (39.1%) groups. The odds ratio for indacterol vs salmeterol was 1.59, p=0.009.

The claim headed a page which featured a bar chart which depicted the results at 26 weeks of Yorgancioglu *et al*. The bar chart showed that at week 26, 47.3% of patients treated with tiotropium had a clinically significant improvement in a quality of life measurement (SGRQ) vs 57.8% in the indacterol 150mcg treated group (p<0.01). There was, however, no significant difference between the percentage of patients achieving a clinically important improvement in the indacterol 300mcg treated group (52.5%) vs the tiotropium group (47.3%).

Yorgancioglu *et al* had shown that at weeks 4, 8 and 26, a statistically significantly greater percentage of patients on indacterol 150mcg achieved a clinically important difference in quality of life (≥4 units) vs tiotropium-treated patients (p<0.01). Only at week 12 was there no statistically significant difference between the two treatment groups. The Panel noted therefore, that in three out of the four time points measured there had been a statistically significant advantage for indacterol 150mcg vs tiotropium. The Panel further noted Novartis' submission that tiotropium reached its maximal effect in 6 months as evidenced by a peak in FEV_1. The Panel thus did not consider that to show the 26 week data was 'cherry picking' as alleged. No breach of Clause 7.2 was ruled.

7 Instructions for use

Page 3 of the leavepiece (the centre panel when opened out) featured five small drawings each showing a different step in the correct use of the Breezhaler device.

COMPLAINT

Boehringer Ingelheim alleged that the diagrams, which were an abridged version of the instructions for use found in the patient information leaflet (PIL) and the SPC implied that the process for use was simpler than it actually was. This was misleading and could cause misunderstandings between patients and prescribers: prescribers might not understand why a patient experienced difficulty with the instructions because they did not appreciate that it was necessary to work through a 13 step process. Boehringer Ingelheim alleged a breach of Clause 7.2.

RESPONSE

Novartis submitted that the 5-step instructions for use were intended to illustrate the mechanism of action of the Breezhaler device and were not a replacement for the full instructions in the PIL and the SPC. Health professionals seen by a Novartis representative would also receive a copy of the SPC and therefore full instructions on inhaler use. Novartis noted that the leavepiece had been reviewed by the MHRA as part of the pre-vetting of all marketing materials at launch. If Boehringer Ingelheim's concerns raised on the apparent basis of protecting patient safety had any merit, the MHRA would not have approved the piece. Novartis denied the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted that the instructions for use had been given in an abbreviated form in the leavepiece; 5 steps had been illustrated compared with the 13 shown in the SPC. The Panel considered that although more instructions would have been helpful, the 5 steps shown were not misleading per se. No breach of Clause 7.2 was ruled.

Complaint received **11 October 2010**

Case completed **15 February 2011**

CASE AUTH/2366/10/10

EX-EMPLOYEE v LILLY

Conduct of representatives and meeting arrangements

An ex-employee of Lilly complained about the conduct of representatives and the arrangements for various meetings in 2008 and 2009.

The detailed response from Lilly is given below.

The complainant noted that an endocrinologist from the US toured a Lilly sales manager's region and presented to diabetologists. The complainant alleged that the sales manager instructed representatives to encourage the doctor to speak about the off-licence use of Byetta in combination with glitazones.

The Panel noted that the slide set used by the doctor contained a slide which read 'Approved Clinical Uses of Byetta'. The second bullet point stated 'Byetta is not approved with glitazone drugs or insulin'. The Panel considered that it was confusing to state, under a heading of 'Approved Clinical Uses' what Byetta was not approved for. The Panel considered that it would have been preferable if the doctor had been given written guidance on how to respond to unsolicited questions about the unlicensed use of Byetta. Nonetheless, the Panel considered that there was no evidence to suggest that representatives had encouraged the doctor to speak about the off-licence use of Byetta in combination with glitazones as alleged. No breaches of the 2006 Code were ruled including Clause 2.

The complainant stated that the same sales manager instructed a representative to contact two diabetes specialist nurses (DSNs). The meeting, in 2008, was at a restaurant and attended by the sales manager, two representatives and the two nurses. The sales manager did not discuss business and made no presentation. The matter was investigated internally and Lilly decided that there was no case to answer.

The Panel noted that for any meeting, held by a pharmaceutical company and attended by health professionals, certain basic principles must apply including, inter alia, the meeting must have a clear educational content and the subsistence provided must be secondary to the nature of the meeting, must be appropriate and not out of proportion to the occasion.

The Panel noted that the meeting at the restaurant had two items for discussion on the agenda. No written agenda had been provided. Five people attended the meeting – three from Lilly and two local DSNs. One of the representatives recorded that the meeting had lasted four hours. The Panel queried the length of the meeting vs the content of the agenda and considered that with regard to balance the meal was out of proportion to the occasion. The Panel was also concerned that the meeting took place in a part of the restaurant open to the public.

The receipt for the meal showed that the bill was paid at 11pm. The cost of the meal, including beverages, was £192 ie £38.40 person. The Panel noted with concern that in Lilly's initial response it had referred to a fixed price menu of between £10.90 and £22 per head. The actual cost was greatly in excess of that and was only provided to the Panel following a request for further information. The Panel considered that this was unacceptable; self regulation relied upon a full and frank disclosure of the facts.

The Panel queried whether the £38.40 per person exceeded that which the two nurses would have paid if they had paid for the meal themselves. The Panel further noted that the bill showed that the group had consumed seven pints of beer, two gins, two whiskies, seven whisky liqueurs and three large glasses of red wine. In the Panel's view this amount of alcohol was excessive and inconsistent with the aims of a business meeting.

The restaurant bill and two taxi fares (assumed to be for the nurses) had been submitted on the expenses of one of the representatives under the heading of 'Group Sells'. The expense account for the evening had been approved by the manager who had been at the meeting. In the Panel's view this was unacceptable; the meeting expenses should have been submitted by the most senior person present ie the manager, for approval by his manager.

The Panel considered that overall, the hospitality provided had been excessive and in that regard it ruled a breach of the Code. The Panel further considered that the manager had not maintained a high standard of ethical conduct. Breaches of the Code were ruled.

The Panel considered that the overall arrangements for the meeting were such as to bring discredit upon the industry. A breach of Clause 2 was ruled.

The complainant stated that in 2009 a Lilly representative left food at a general hospital diabetes department without any educational presentation. The representative spoke to one nurse and asked her to let the others know that she would put them down for a meeting that day if they should be asked.

The Panel noted that the representative had arrived at the hospital with sufficient food for her pre-

planned meeting. The meeting was a group sell event and the cost of the food was approximately £11 per head. Four nurses had previously confirmed their attendance but on the day only one turned up. The Panel noted that the representative had stayed as long as possible, waiting for the other three nurses to arrive. The Panel further noted Lilly's submission that during that time the representative had a product discussion with the one nurse using approved sales material. Eventually the representative had left, leaving the remainder of the food for the nurses who had not turned up.

The Panel considered that the circumstances were unfortunate but the fact that one nurse turned up supported the fact that a meeting had been planned. It also appeared that the representative and the one nurse discussed a product as planned, ate some of the food and the remainder was left for the other three.

The Panel considered that, although within the Lilly guidelines, the cost of the hospitality for a lunchtime meeting was on the outer limits of acceptability. Nonetheless the Panel considered that the arrangements were not unacceptable. It was unfortunate that only one of the intended audience had turned up. Nonetheless a product was discussed with that one nurse. The Panel considered that the representative had maintained a high standard of ethical conduct. Only the remainder of the food had been left. No breaches of the Code were ruled including Clause 2.

Upon appeal by the complainant the Appeal Board noted Lilly's submissions that in advance of the pre-planned meeting, the sales representative had entered the names of the four nurses who she had expected to attend, into the customer relations management (CRM) system. On the day of the meeting, the representative had arrived with sufficient food for the meeting. Of the four nurses expected, one turned up. Whilst waiting as long as possible for the others to arrive, and before she had to leave for another meeting, the representative had discussed a product with the one nurse using approved sales material.

The Appeal Board was very concerned to note that it was revealed in Lilly's response to the appeal, that before leaving the meeting, the representative had asked the one nurse that attended whether it would be acceptable for her to include the other nurses' names on the CRM system as attendees, as a way to justify the food expenditure to Lilly.

The Appeal Board noted that the complainant had submitted that the senior DSN had contacted him after the meeting because she was furious about the representative's conduct and because the DSN who had attended the meeting was new and inexperienced. The complainant further alleged that there had been no product discussion at the meeting.

Lilly had submitted that in subsequent email correspondence between the sales representative and the senior DSN, the senior DSN had accepted the representative's apology. Nonetheless, the Appeal Board noted that the names of the three nurses (including the senior DSN) that had not attended the meeting had remained on the CRM system.

The Appeal Board was concerned to note from Lilly's representative at the appeal that, in the course of the representative's disciplinary procedure, further details about the meeting had emerged including that the senior DSN had been at least upset, if not furious as alleged by the complainant. This was in contrast to Lilly's statement in response to the appeal that the nature of the senior DSN's reaction was new information, not previously available to Lilly. It appeared that some people in Lilly knew that the senior DSN had been at the least upset before the Panel had made its ruling in this case, but the information had not been given to those within the company dealing with the complaint. The Appeal Board was concerned that lack of communication within Lilly meant that it had not provided more complete information to the Panel; self regulation relied on full and frank disclosure. The Appeal Board asked that Lilly be advised of its concerns in this regard.

The Appeal Board noted that both parties agreed that the senior DSN had been upset, albeit to a greater or lesser extent, by the representative's conduct. The Appeal Board considered that the representative's actions in asking the one nurse who had attended to collude with her in recording the attendance of the three other nurses in order to justify the expenditure on the food was entirely inappropriate. The Appeal Board considered that the representative had failed to maintain a high standard of ethical conduct and a breach of the Code was ruled. The appeal on this point was successful.

The Appeal Board was concerned that the senior DSN had been upset by the representative. The Appeal Board ruled that high standards had not been maintained in a breach of the Code. The appeal on this point was successful.

The Appeal Board noted that the complainant and Lilly differed as to whether a product discussion had taken place between the representative and the nurse. There was insufficient evidence to support either party and thus the Appeal Board considered that the complainant had not proved this part of his complaint on the balance of probabilities. The Appeal Board considered that, although within the Lilly guidelines, the cost of the hospitality for a lunchtime meeting was on the outer limits of acceptability. Further, the Appeal Board considered that the food had been purchased on the basis of the reasonable expectation that four nurses would attend. The representative had not been informed beforehand that three of the nurses would not attend. This was most unfortunate and left the representative to decide what to do with the excess food; on the particular facts of this case, including the relatively small amount involved, the

Appeal Board decided that the arrangements were not unacceptable. The Appeal Board upheld the Panel's ruling of no breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above, however it considered that the circumstances did not warrant a ruling of a breach of Clause 2. The Appeal Board upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was unsuccessful.

An ex-employee of Eli Lilly and Company Limited complained about the conduct of representatives and the arrangements for various meetings in 2008 and 2009.

1 Alleged off-licence promotion

COMPLAINT

The complainant noted that an endocrinologist from the US toured a Lilly district sales manager's region and presented to diabetologists. The complainant alleged that the district sales manager instructed representatives to encourage the doctor to speak about the off-licence use of Byetta in combination with glitazones. The complainant noted that it was not in the representatives' interests to admit to this.

The Authority asked Lilly to respond in relation to Clauses 2, 3.2 and 15.2 of the 2008 Code for meetings on and after 1 July. For meetings prior to 1 July, the company was asked to consider the same clauses in the 2006 Code.

RESPONSE

Lilly stated that it invited an endocrinologist to conduct a speaker tour in June 2008.

Lilly's standard practice was for US speaker tours to be organised from the US through a third party with representatives in the local affiliate co-ordinating the local meetings.

The speaker tour comprised five promotional meetings and the endocrinologist was invited to share her experiences of treating patients with Byetta with the invited health professionals. The endocrinologist attended meetings in June. Between four and ten health professionals attended each meeting; the costs ranged from £250 to £1,380. Lilly provided a spreadsheet with information taken from its customer relations management (CRM) system in relation to these three meetings.

At each meeting, the endocrinologist presented on the topic of 'Using Byetta in Family Practice' and copies of her slides together with the current Byetta summary of product characteristics (SPC) were provided. Slide 5 made it clear that 'Byetta [was] approved for use with metformin and sulfonylurea' as per its licence and '… not approved with glitazone drugs or insulin'. These slides were reviewed and approved on email by a Lilly clinical research physician, before any presentation was given.

In order to respond to the complaint about its district sales manager, Lilly had spoken to him and a representative and asked both for their recollection of events. The representative advised that:

'When I briefed [the endocrinologist] pre-tour … I also mentioned that there could well be off-label questions, certainly around use with insulin, and that whilst she should feel free to respond as she would with any other medical audience, she must re-enforce that it was off-label.'

With regard to the allegation that Lilly's district sales manager encouraged his representatives to encourage the endocrinologist to speak off-licence, Lilly's representative responded that:

'… at no time in the long planning process did John ever touch upon or allude to the benefits of guiding/encouraging [the endocrinologist]' focus upon her experience of patients using Byetta off-label. Nor indeed was there any intimation from [the endocrinologist] that health professionals be encouraged to post questions addressing this same thing'.

A supporting email was provided.

The district sales manager also denied the allegation, and had advised that he did not attend any of the meetings at which the endocrinologist presented.

The facts had been further corroborated by four other members of the district sales manager's team who were all present at the time of the doctor's speaker tour.

For these reasons, Lilly denied any breach of Clauses 2, 3.2 and 15.2 of the 2006 Code in relation to this speaker tour or the sales manager's conduct in connection with it. There was no off-label promotion of Byetta.

PANEL RULING

The Panel noted that the slide set used by the endocrinologist contained a slide which read 'Approved Clinical Uses of Byetta'. The second bullet point stated 'Byetta is not approved with glitazone drugs or insulin'. The Panel considered that it was confusing to state, under a heading of 'Approved Clinical Uses' what Byetta was not approved for. The Panel considered that it would have been preferable if the endocrinologist had been given written guidance on how to respond to unsolicited questions about the unlicensed use of Byetta. Nonetheless, the Panel considered that there was no evidence to suggest that representatives had encouraged the endocrinologist to speak about the off-licence use of Byetta in combination with glitazones as alleged. No breach of Clauses 3.2 and 15.2 of the 2006 Code was ruled.

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

2 Alleged excessive hospitality

COMPLAINT

The complainant stated that the Lilly's district sales manager instructed a Lilly sales representative to contact two diabetes specialist nurses (DSNs). The meeting was at an Indian restaurant in October 2008. In attendance were the district sales manager, two Lilly sales representatives and the two nurses. The sales manager did not discuss business and made no presentation. The matter was investigated internally and Lilly decided that there was no case to answer.

The Authority asked Lilly to respond in relation to Clauses 2, 9.1, 15.2 and 19.1 of the 2008 Code.

RESPONSE

Lilly submitted that in 2008, its district sales manager attended an evening meeting with two Lilly sales representatives and two nurses. Lilly's sales manager had asked one of its sales representatives to set up this meeting on a number of occasions before the meeting. The evening meeting was conducted over a meal at an Indian restaurant. There were two items on the agenda for discussion. The first was the suitability of a service that Lilly provided to general practice ('Enhanced Management of Type 2 Diabetes') for which the two nurses would have responsibility for utilising as community DSNs. The second was Lilly's local and national representative training programmes, which both nurses assisted with, and to seek feedback on the curriculum development and training methods deployed. There was no product discussion or promotion at this meeting, indeed it was not set up as a promotional meeting. The meeting took place downstairs in a discreet alcove of the restaurant and currently the fixed price menu at this restaurant varied from £10.90 to £22 per head.

In a disciplinary meeting in December 2008, following which he was dismissed, one of Lilly's sales representatives expressed reservations about the meeting; he believed that taking customers for a meal which was to be paid for by Lilly breached Lilly standard operating procedures (SOPs) and as such was a breach of the Code. He claimed that he had refused to pay for the meal as a result of these concerns. Given the seriousness of the allegation of misconduct that the representative made against his manager, and a sales representative colleague the matter was investigated with Lilly's disciplinary process.

A senior Lilly manager investigated and chaired the disciplinary hearings. He found the allegations to be unsubstantiated, that there was a legitimate business need to meet with the nurses and that with regard to the content of the conversation there was nothing to answer. The meeting was therefore deemed to comply with Lilly's SOPs and therefore the Code. Lilly provided notes from its district sales manager's disciplinary hearing and the letter confirming the outcome.

Lilly denied breaches of Clauses 2, 9.1, 15.2 or 19.1 of the 2008 Code.

In response to a request for further information Lilly submitted that its representative's entry for the meeting indicated that it started at 7.30pm and lasted four hours, with a total cost of £192 for 5 attendees, a copy of the receipt was provided. Such hospitality as was provided was secondary to the purpose of the meeting.

Lilly further submitted that there was no hospitality associated with this meeting before or afterwards as demonstrated through the expense reports submitted by the three Lilly attendees (copies were provided). Its district sales manager and its representative making the above allegations met earlier that day at a hotel, however this was not in connection with the meeting held later that evening.

As to the content of the meeting, the discussion focussed on two areas; service development within the local health board and, more specifically, how Lilly's Enhanced Management of Type 2 Diabetes service could assist the NHS with the implementation of this service redesign, and secondly, training support for Lilly sales representatives.

Regarding service development within the local health board, the purpose of this discussion was to understand the timelines, processes and roles and responsibilities of key stakeholders (clinicians and payers) in the transfer of diabetes services from the acute setting into the community. As community DSNs the two nurses were ideally placed to help Lilly understand how this service redesign impacted the local healthcare community.

Lilly noted that its Enhanced Management of Type 2 Diabetes service had been developed in conjunction with, and was delivered by, a third party, National Services for Health Improvements ('NSHI'). The service was a non-promotional therapeutic and clinical review service and was available to GPs to help enhance their management of patients with type 2 diabetes. It had run since April 2008 and over 900 practices had used the service since launch. Lilly provided a copy of the booklet available to GPs giving precise details of this service. This booklet was not referred to or used during the course of the discussion.

Regarding training support for Lilly representatives, Lilly noted that the two nurses had been involved in the development and implementation of Lilly's internal training curriculum through Lilly's 'Selling Capability Workshops'. One of the nurses advised on the content of the training curriculum and assessed the workshops, and the other nurse played the role of an assessor during the training workshops in the Summer of 2008. The purpose of the training discussion at this meeting was to gain greater insight into the workshops and how they could be improved. No materials were used during the course of the discussion.

Lilly acknowledged that its representative's entry in the customer relations management (CRM) system described the meeting as 'Discussion service development within the local health board with regards to moving Byetta into community in conjunction with 2 new cons posts'. Lilly had confirmed with its sales manager and its representative that there was no product discussion or promotion at this meeting, and the reference to 'Byetta' in the entry should, in fact, be to 'diabetes' given that the discussion was about moving diabetes services into the community. Lilly's representative had been fully trained on the CRM system and knew that this was not how Lilly expected a meeting of this nature to be recorded.

Lilly noted that it had recently refreshed its sales force training on 'Sales vs Service', which included information on how service calls could not be combined with any reference to product, as well as how to accurately record these two distinct calls in the system.

PANEL RULING

The Panel noted that for any meeting, held by a pharmaceutical company and attended by health professionals, certain basic principals must apply including, inter alia, the meeting must have a clear educational content and the subsistence provided must be secondary to the nature of the meeting, must be appropriate and not out of proportion to the occasion.

The Panel noted that the meeting at the Indian restaurant had two items for discussion on the agenda. No written agenda had been provided. Five people attended the meeting – three from Lilly and two local diabetes specialist nurses. One of the representatives who attended the meeting recorded on the CRM system that the meeting had lasted four hours. The Panel queried the length of the meeting vs the content of the agenda and considered that with regard to balance the meal was out of proportion to the occasion. The Panel was also concerned that the meeting took place in a part of the restaurant which was open to the public, albeit in an alcove.

The receipt for the meal showed that the bill was paid at 11pm. The cost of the meal, including beverages, was £192 ie £38.40 person. The Panel noted with concern that in Lilly's initial response it had referred to a fixed price menu of between £10.90 and £22 per head. The actual cost was greatly in excess of that and was only provided to the Panel following a request for further information. The Panel considered that this was unacceptable; self regulation relied upon a full and frank disclosure of the facts.

The Panel queried whether the £38.40 per person exceeded that which the two nurses would have paid if they had paid for the meal themselves. The Panel further noted that the bill showed that the group had consumed seven pints of beer, two gins, two whiskies, seven whisky liqueurs and three large glasses of red wine. In the Panel's view this amount of alcohol was excessive and inconsistent with the aims of a business meeting.

The restaurant bill had been submitted on the expenses of one of the representatives under the heading of 'Group Sells'. The representative had also submitted two taxi fares from that evening which the Panel assumed were for the two nurses. The taxi fares totalled £35. The expense account for the evening had been approved by the manager who had been at the meeting. In the Panel's view this was unacceptable; the meeting expenses should have been submitted by the most senior person present ie the district sales manager, for approval by his manager.

The Panel considered that overall, the hospitality provided had been excessive and in that regard it ruled a breach of Clause 19.1.

The Panel noted that two months' later, at his own disciplinary hearing, one of the representatives had expressed reservations about the meeting and claimed to have refused to pay for the meal because of those concerns. The Panel considered that on the balance of probabilities on the evening in question and with regard to the submission of expenses, the representatives would have followed instructions from their manager. The Panel considered that the manager had not maintained a high standard of ethical conduct. Breaches of Clauses 15.2 and 9.1 were ruled.

The Panel considered that the overall arrangements for the meeting were such as to bring discredit upon the industry. A breach of Clause 2 was ruled.

3 Alleged inappropriate hospitality

COMPLAINT

The complainant stated that in 2009 a Lilly sales representative, left food at a general hospital diabetes department without any educational presentation. The sales representative spoke to one nurse and asked her to let the others know that she would put them down for a meeting that day if they should be asked.

The Authority asked Lilly to respond in relation to Clauses 2, 9.1, 15.2 and 19.1 of the 2008 Code of Practice.

RESPONSE

Lilly stated that given that there was little detail in this allegation, it had examined its CRM system to identify when its sales representative attended the general hospital in 2009. Lilly had also spoken with its sales representative directly; she remembered this meeting well.

The meeting which Lilly believed the complainant referred to was a lunchtime group sell promotional meeting arranged for a date in May 2009. The

meeting was scheduled to start at 12:30pm and four nurses were confirmed to attend. The representative called the week before to confirm the start time and number of attendees to ensure that she brought the correct amount of food with her. The representative spent £56.54 on food for the meeting which was within Lilly's guidelines of £12 per head for hospitality at group sell meetings.

When the representative arrived to set up the lunch at the diabetes unit, only one of the four nurses joined her as the other three were with patients in other parts of the hospital. The representative had a product discussion with the nurse, using approved sales materials, and then waited for the others to arrive. By 1:40pm, when the representative had to leave the hospital for another appointment, the three other nurses had not returned to the diabetes unit. The representative therefore decided to leave the remainder of the food for them.

Lilly provided a copy of the relevant entry from its CRM system which showed the four nurses who the representative anticipated meeting that day.

Lilly thus disputed the complainant's version of events and accordingly denied all and any allegation that there had been a breach of Clauses 2, 9.1, 15.2 or 19.1 of the 2008 Code in relation to the meeting or the representative's conduct in connection with it.

In conclusion, Lilly was cognisant of its responsibilities with respect of the Code and considered its representatives to be at the core of its business in line with the Code. The company therefore expected each and every activity conducted by a representative to comply with the Code and to be of the highest standard and quality.

In response to a request for further information Lilly submitted that the representative set up the meeting in the CRM system before the meeting date. She had received verbal confirmation the week before the meeting that four of her key customers would attend and this is what she entered into the system. As the cost per head was under £12 and within Lilly's guidelines for hospitality provision at group sell meetings, the meeting did not need to be pre-approved by her line manager.

As explained above, the representative attended the diabetes unit at the hospital and set up the lunch but only one of the nurses joined her as the other three were busy elsewhere. The representative should have taken those three nurses out of the meeting entry in the CRM system before she submitted it; she did not and admitted that this was an error on her part. Disciplinary action was being taken in this respect.

PANEL RULING

The Panel noted that the representative had arrived at the hospital with sufficient food for her pre-planned meeting. The meeting was a group sell event and the cost of the food was approximately £11 per head. Four nurses had previously confirmed their attendance but on the day only one turned up. The Panel noted that the representative had stayed as long as possible, waiting for the other three nurses to arrive. The Panel further noted Lilly's submission that during that time the representative had a product discussion with the one nurse using approved sales material. Eventually the representative had left, leaving the remainder of the food for the nurses who had not turned up.

The Panel considered that the circumstances were unfortunate but the fact that one nurse turned up supported the fact that a meeting had been planned. It also appeared that the representative and the one nurse discussed a product as planned, ate some of the food and the remainder was left for the other three.

The Panel considered that, although within the Lilly guidelines, the cost of the hospitality for a lunchtime meeting was on the outer limits of acceptability. Nonetheless the Panel considered that the arrangements were not unacceptable. It was unfortunate that only one of the intended audience had turned up. Nonetheless a product was discussed with that one nurse and so the Panel ruled no breach of Clause 19.1. The Panel considered that the representative had maintained a high standard of ethical conduct. Only the remainder of the food had been left. No breach of Clauses 15.2 and 9.1 was ruled. These rulings were appealed.

The Panel noted its rulings above and ruled no breach of Clause 2. This ruling was appealed.

APPEAL BY THE COMPLAINANT

The complainant submitted that the senior diabetes specialist nurse (DSN) at the diabetes unit at the general hospital, contacted him after the meeting because she was furious about the representative's conduct. The senior DSN acknowledged that the representative had organised the meeting but that on the day the department was exceptionally busy. Only the newly in place (2 weeks) DSN was in the department and she explained that she was too busy to attend the meeting as were colleagues. The representative stated that that was not a problem, she would leave the food and just let the others know that she did so and that she could put their names down for the day. The senior DSN left the department with no product discussion because the nurse did not have time. The senior DSN was furious because the new nurse was inexperienced and did not know what to do and was concerned over the situation. The senior DSN felt that this was grossly unfair on her new colleague. Finally on this point, having worked at that time with Lilly's CRM, representatives did not add the attendees at a meeting until after the meeting, not as stated by the representative prior to the meeting and well Lilly knew that. The complainant was confident that the DSNs, if questioned, would confirm this. The complainant appealed all of the Panel's rulings.

COMMENTS FROM LILLY

Lilly noted that the fact that the senior DSN had contacted the complainant after the group sell lunchtime meeting in May 2009, 'furious about the sales representative's conduct', was new information which was not raised in the complaint and had not previously been made available to Lilly.

Lilly understood from the representative that the senior DSN did not raise any concerns with her about the group sell meeting at the time. In to respond to these new claims, the representative had been extensively questioned on the matters now raised and Lilly's understanding of the matter was:

- In early June 2009, several weeks after the group sell meeting, the representative emailed the senior DSN to determine whether it would be possible to meet the health professionals in the diabetes unit individually, rather than organising a group sell meeting; the department was clearly very busy and so it was difficult to get a group together. The senior DSN responded a couple of days later and told her that, in accordance with the department's policy, the representative must meet the health professionals in a group sell setting, not individually.
- The senior DSN went on to state that she felt the representative had compromised staff at the group sell meeting in May because the representative had asked the DSN with whom she had had a product discussion, when the other nurses were expected to return to the department, the DSN being 'new' to the department. The representative understood that the DSN to whom she spoke on that day had in fact worked in the diabetes unit for some time as a trainee DSN.
- Lilly submitted that as explained previously, the representative had expected four nurses to attend the meeting, and had entered their names into the CRM system in advance of the meeting. The CRM system allowed meeting details, including expected attendees, to be entered in the system before a meeting took place, not as the complainant alleged (viz: 'representatives did not add the attendees at a meeting until after the meeting …'). As the representative had telephoned the diabetes unit the week before the meeting to confirm the arrangements, and expected attendees, it was appropriate for her to fill in the CRM record for that meeting. As it turned out, only one of the four nurses was able to attend as the other three were with patients in another part of the hospital. The representative was advised that the three other nurses would probably return after she was due to leave for another pre-arranged appointment. On this basis, and as previously explained, the representative decided to leave the remaining food for those nurses. As she was leaving the food, the sales representative asked the DSN whether it would be acceptable for her to include the other nurses' names in the CRM system as having attended, as a way to justify the food expenditure to Lilly. The senior DSN felt that this question had been unfair of the representative and had compromised the DSN.
- On hearing of her concerns, the representative immediately apologised to the senior DSN. The senior DSN accepted the apology and offered to talk to Lilly's district sales manager, to explain why her staff had been busy on the day of the group sell meeting and unable to attend.
- Lilly submitted that, as explained previously, and following further discussions with the representative since, she acknowledged that it was not appropriate that the three nurses' names remained in the CRM system as attendees when they were not at the meeting. The names should have been removed as the CRM system allowed meeting details to be amended after the event. The representative had admitted that this was an error on her part and she now recognised that the question she asked the DSN was inappropriate.
- Disciplinary action had been taken against the representative in respect of the above, the outcome was communicated to her in December 2010.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant submitted that he knew the truth but was unable to prove it. The complainant refuted Lilly's claims in its primary statements and noticed that in its revised statements the facts changed (ie original version of why names were included then revised which he noticed was closer to his own understanding). Lilly continued to have people believe that it was an ethical company.

APPEAL BOARD RULING

Upon appeal from the complainant the Appeal Board noted Lilly's submissions that in advance of the pre-planned meeting, the representative had entered the names of the four nurses who she had expected to attend, into the Lilly CRM system. On the day of the meeting, the representative had arrived at the hospital with sufficient food for the meeting. The meeting was a group sell event and the cost of the food was approximately £11 per head. Of the four nurses expected, one turned up. Whilst waiting as long as possible for the others to arrive, and before she had to leave for another meeting, the representative had discussed a product with the one nurse using approved sales material.

The Appeal Board was very concerned to note that it was revealed in Lilly's response to the appeal, that before leaving the meeting, the representative had asked the one nurse that attended whether it would be acceptable for her to include the other nurses' names on the CRM system as attendees, as a way to justify the food expenditure to Lilly.

The Appeal Board noted that the complainant had submitted that the senior DSN, the senior DSN, had contacted him after the meeting because she was furious about the representative's conduct and

because the DSN who had attended the meeting was a new and inexperienced nurse. The complainant further alleged that there had been no product discussion at the meeting.
Lilly had submitted that in subsequent email correspondence between the representative and the senior DSN, the senior DSN had accepted the representative's apology. Nonetheless, the Appeal Board noted that the names of the three nurses (including the senior DSN) that had not attended the meeting had remained on the CRM system.
The Appeal Board was concerned to note from Lilly's representative at the appeal that, in the course of the representative's disciplinary procedure, further details about the group sell meeting had emerged including the fact that the senior DSN had been at least upset, if not furious as alleged by the complainant. This was in contrast to Lilly's statement in response to the appeal that the nature of the senior DSN's reaction was new information, not previously available to Lilly. It appeared that some people in Lilly knew that the senior DSN had been at the least upset before the Panel had made its ruling in this case, but the information had not been given to those within the company dealing with the complaint. The Appeal Board was concerned that lack of communication within Lilly meant that it had not provided more complete information to the Panel; self regulation relied on full and frank disclosure. The Appeal Board asked that Lilly be advised of its concerns in this regard.

The Appeal Board noted that both parties agreed that the senior DSN had been upset, albeit to a greater or lesser extent, by the sales representative's conduct. The Appeal Board considered that the sales representative's actions in asking the one nurse who had attended the lunchtime meeting to collude with her in recording the attendance of the three other nurses in order to justify the expenditure on the food was entirely inappropriate. The Appeal Board considered that the representative had failed to maintain a high standard of ethical conduct and a breach of Clause 15.2 was ruled. The appeal on this point was successful.

The Appeal Board was concerned that the senior DSN had been upset by the representative. The Appeal Board considered that high standards had not been maintained and it ruled a breach of Clause 9.1. The appeal on this point was successful.

The Appeal Board noted that there was a difference between the complainant and Lilly as to whether or not a product discussion had taken place between the representative and the nurse. There was insufficient evidence to support either party and thus the Appeal Board considered that the complainant had not proved this part of his complaint on the balance of probabilities. The Appeal Board considered that, although within the Lilly guidelines, the cost of the hospitality for a lunchtime meeting was on the outer limits of acceptability. Further, the Appeal Board considered that the food had been purchased on the basis of the reasonable expectation that four nurses would attend. The representative had not been informed beforehand that three of the nurses would not attend. This was most unfortunate and left the representative to decide what to do with the excess food; on the particular facts of this case, including the relatively small amount involved, the Appeal Board decided that the arrangements were not unacceptable. The Appeal Board upheld the Panel's ruling of no breach of Clause 19.1. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above, however it considered that the circumstances did not warrant a ruling of a breach of Clause 2. The Appeal Board upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **21 October 2010**

Case completed **8 April 2011**

CASE AUTH/2367/10/10

GENERAL PRACTICTIONER AND GP PRESCRIBING LEAD v TAKEDA

Use of inverted black triangle

A general practitioner and GP prescribing lead, complained about a two page advertisement for Amias (candesartan), issued by Takeda, which had appeared in 'Guidelines in Practice', October 2010. The advertisement featured a table of data comparing clinical aspects of the use of candesartan, losartan and valsartan. One of the aspects compared was whether the medicines were subject to special reporting requirements with regard to adverse events ie were they 'black triangle' medicines? The table showed that both losartan and valsartan were black triangle medicines whereas candesartan was not.

The complainant stated that the first page of the advertisement was misleading. The advertisement placed a black triangle next to the generic name losartan. Generic losartan did not carry a black triangle warning in the BNF while Cozaar, the branded product did. The reference clarifying that the triangle related to the branded product was on the second page of the advertisement. The complainant alleged that the advertisement was misleading as it suggested that losartan was a black triangle medicine which was not so.

The detailed response from Takeda is given below.

The Panel noted that the advertisement was headed 'The Facts: ARBs [angiotensin receptor blockers] in Chronic Heart Failure'. The Panel noted Takeda's submission that a black triangle had been reinstated on Cozaar when it was approved for use in patients with chronic heart failure.

The Panel noted from the electronic medicines compendium (www.medicines.org.uk) that generic forms of losartan were now available. The summary of product characteristics (SPCs) for these generics stated that they were indicated for chronic heart failure but did not indicate that they were black triangle medicines.

The Panel considered that the position was confusing. The list included in the MHRA's list of new drugs under intensive surveillance, October 2010, was not clear as to whether the black triangle for losartan applied to the generic form or only to the brand ie Cozaar. If the black triangle had been reinstated on Cozaar when it was approved for use in chronic heart failure then it would seem logical to expect all forms of losartan so indicated to also carry the black triangle. In a publication from the MHRA, 'New drugs and vaccines under intensive surveillance' the Agency requested emails from companies if they held marketing authorizations for a medicine that had had a black triangle reinstated. The Panel had no way of knowing if the manufacturers of generic losartan had emailed the MHRA and the outcome of such communication. By whatever means it appeared that the generic losartans, although approved for use in heart failure, were not black triangle medicines. Conversely, however, the advertisement implied that all forms of losartan were black triangle medicines. An asterisk beside the symbol referred the reader to a list of references which appeared overleaf and which made it clear that the black triangle related to the Cozaar SPC. The Panel noted that the claims could not be qualified by the use of a footnote or the like. The Panel thus considered that the implication that all forms of losartan were black triangle medicines was misleading and in that regard it ruled a breach of the Code.

Upon appeal by Takeda the Appeal Board noted that the first page of the two page advertisement featured a table in which six clinical attributes of the use of candesartan, losartan and valsartan in heart failure were compared. For the most part, ticks were shown for candesartan and crosses for losartan and valsartan. The seventh and final attribute to be compared was 'Black triangle drug' for which candesartan received a cross and losartan and valsartan each received a tick. In the column headings to the table, losartan and valsartan each had a black triangle next to their name. In the Appeal Board's view, Takeda had chosen to highlight the possession, or otherwise, of a black triangle as a means to differentiate the products. The Appeal Board noted that the Code did not require companies to display the black triangle against the names of competitor products. If, however, they chose to do so it must be in a manner which complied with the Code. The Appeal Board considered that the overall aim of the advertisement was to encourage the prescription of Amias, not the reporting of adverse events with losartan or valsartan. By highlighting the black triangle status of the three medicines, prescribers might be inclined to favour candesartan because it was not subject to enhanced surveillance and in that regard might be perceived by some to have patient safety benefits.

The Appeal Board noted that the black triangle status of generic losartan was confusing and appeared illogical given that branded losartan (Cozaar) was subject to enhanced surveillance. The Appeal Board noted Takeda's submission that as the black triangle could now be reinstated for well established medicines which received a new

indication, there was a possibility that such reinstatement could still be in place when generic versions became available. Takeda accepted that there was an inconsistency in the labelling of generic losartan. The complainant had pointed out that generic losartan did not carry a black triangle warning in the BNF whereas Cozaar did.

The Appeal Board was concerned about patient safety but considered that its role was to consider the matter in relation to the Code which required information and claims in advertisements to be accurate. Contrary to the impression given by the advertisement at issue not all formulations of losartan were officially designated as black triangle medicines. Although the black triangle next to losartan in the table heading was referenced to the Cozaar SPC, the Appeal Board noted that claims could not be qualified by footnotes and the like. The Appeal Board considered that the advertisement was misleading as alleged and upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Panel noted that the Code required that where the pages of a two page advertisement were not facing, neither must be false or misleading when read in isolation. The Panel noted that the reference to the Cozaar SPC was overleaf from the table of data in question and further noted its comments above about the use of footnotes to qualify claims. However, given its ruling of a breach of the Code in relation to page 1 of the advertisement, the Panel did not consider that this meant that it was false or misleading when read in isolation. No breach of the Code was ruled.

The Panel noted that the advertisement in question was not an abbreviated advertisement and thus no breach of the requirements of the Code in that regard was ruled.

The Panel noted that prescribing information was an integral part of the advertisement and was included on the second page. No breach of the Code was ruled.

A general practitioner and GP prescribing lead, complained about a two page advertisement (ref TA101054) for Amias (candesartan), issued by Takeda UK Ltd, which had appeared in 'Guidelines in Practice', October 2010. The advertisement featured a table of data comparing clinical aspects of the use of candesartan, losartan and valsartan. One of the aspects compared was whether the medicines were subject to special reporting requirements with regard to adverse events ie were they 'black triangle' medicines? The table showed that both losartan and valsartan were black triangle medicines whereas candesartan was not.

COMPLAINT

The complainant stated that the first page of the advertisement was misleading and breached Clauses 6.1, 7.2, and possibly 5.7, of the Code.

The advertisement placed a black triangle next to the generic name losartan. Generic losartan did not carry a black triangle warning in the BNF while Cozaar, the branded product did. The reference clarifying that the triangle related to the branded product was on the second page of the advertisement.

The complainant alleged that the advertisement was misleading as it suggested that losartan was a black triangle medicine which was not so.

When writing to Takeda, the Authority asked it to respond in relation to Clause 4.1 of the Code in addition to the clauses cited by the complainant.

RESPONSE

Takeda stated that it was concerned that a health professional considered that the advertisement was misleading and it took this allegation very seriously. It was not Takeda's intention for any of its materials to be misleading and it had thoroughly reviewed the advertisement at issue with particular focus on Clauses 7.2, 6.1 and 5.7. The Authority requested that Takeda also consider the requirements of Clause 4.1. As the complaint was about the use of the black triangle symbol, Takeda wondered if this was a typographical error and should be Clause 4.11. Takeda therefore responded in relation to both Clauses 4.1 and 4.11.

The advertisement in question was a double-sided insert within Guidelines in Practice. On the first page of the advertisement there was a table which included information on the three angiotensin receptor blockers licensed for chronic heart failure (candesartan, losartan and valsartan). A black triangle had been placed beside losartan and valsartan. The complainant had stated that only the Cozaar brand of losartan (Merck Sharp and Dohme) was a black triangle medicine and that the generic versions did not have black triangle status. The information in the table was supported by a reference to the summary of product characteristics (SPC) for Cozaar although in line with Clauses 7.4 and 7.6 there was no absolute requirement to include a reference as the information was not from a published study and therefore Takeda would just be required to substantiate the information if requested.

Takeda stated that for several reasons, it did not agree that only the branded (Cozaar) version of losartan was a black triangle medicine whilst the generic versions were not:

- Within the information provided by the Medicines and Healthcare products Regulatory Agency (MHRA) on black triangle medicines it was clear that it related to an *'active substance'* and not any particular brand or preparation.

- A black triangle could be reinstated to a previously licensed active substance if it had a significant new indication which altered the

established risk/benefit profile or it was approved for use in a new patient population. For losartan (and valsartan), the black triangle was reinstated following the approval of its use in chronic heart failure. The MHRA even included losartan (Cozaar) as an example when explaining about the reinstatement of the black triangle in established medicines. When the black triangle was reinstated for losartan, it was still under patent protection and therefore only available as Cozaar. The patent for Cozaar had since expired, however the MHRA could not be expected to track and follow the patent status for all branded medicines and thus the availability of generic versions. As it was clear that the black triangle related to the *active substance*, rather than a particular brand or preparation, the fact that the MHRA referred to Cozaar was irrelevant.

- The MHRA published a monthly list of all black triangle medicines by trade name and by generic name. As the generic versions did not have a brand name, only Cozaar was listed under trade name.

- The MHRA clearly requested to be emailed by *any* company that held the marketing authorization for a medicine that had the black triangle reinstated due to the product being approved for use in a significantly new indication. This would apply to all companies (including generic companies) that held a marketing authorization for losartan. If a generic company had not done this (and therefore did not show the black triangle on its SPC) it did not negate the fact that the active medicine, losartan, had a black triangle and was subject to enhanced surveillance.

- Importantly, when a generic company applied for a marketing authorization for a generic version of a branded medicine it did so by demonstrating that the generic version was equivalent to the branded version. Once bioequivalence had been demonstrated the company could bridge all the clinical data for the branded version and apply it to the generic version. It would seem only appropriate that any enhanced safety requirements also applied to these bioequivalent generic versions.

- Takeda noted that the purpose of the black triangle being reinstated to an established medicine was to confirm the risk/benefit profile when used in a new indication. This was to ensure patient safety. When GPs prescribed any medicine they generally did so by writing the generic name for that medicine (rather than a brand name). GPs would not know which version of losartan (Cozaar or one of the generics) was actually dispensed to the patient at the pharmacy. It was therefore important that all suspected adverse reactions associated with the use of losartan (generic or branded) in heart failure were reported.

Takeda thus did not believe the advertisement was misleading and in breach of Clauses 6.1, 7.2 and 4.11 as alleged. Furthermore, as this advertisement was not an abbreviated advertisement and prescribing information (which was clear and legible) was provided Takeda did not believe it to be in breach of Clauses 5.7 or 4.1.

PANEL RULING

The Panel noted that the advertisement was headed 'The Facts: ARBs [angiotensin receptor blockers] in Chronic Heart Failure'. The Panel noted Takeda's submission that a black triangle had been reinstated on Cozaar when it was approved for use in patients with chronic heart failure. The Cozaar summary of product characteristics (SPC) stated that the usual initial dose of losartan in heart failure was 12.5mg once daily. The dose should generally be titrated at weekly intervals (ie 12.5mg daily, 25mg daily, 50mg daily) to the usual maintenance dose of 50mg once daily, as tolerated by the patient. Cozaar was available in tablets of 12.5mg, 25mg, 50mg and 100mg.

The Panel noted from the electronic medicines compendium (www.medicines.org.uk) that generic forms of losartan were now available. From a practical point of view some of these could not be used to initiate treatment in chronic heart failure given that generic tablets of 12.5mg were not available. The SPCs for these generics, however, did state that they were indicated for chronic heart failure but did not indicate that they were black triangle medicines.

The Panel considered that the position was confusing. The list included in the MHRA's list of new drugs under intensive surveillance, October 2010, was not clear as to whether the black triangle for losartan applied to the generic form or only to the brand ie Cozaar. If the black triangle had been reinstated on Cozaar when it was approved for use in chronic heart failure then it would seem logical to expect all forms of losartan so indicated to also carry the black triangle. In a publication from the MHRA, 'New drugs and vaccines under intensive surveillance' the Agency requested emails from companies if they held marketing authorizations for a medicine that had had a black triangle reinstated. The Panel had no way of knowing if the manufacturers of generic losartan had emailed the MHRA and the outcome of such communication. By whatever means it appeared that the generic losartans, although approved for use in heart failure, were not black triangle medicines. Conversely, however, the advertisement implied that all forms of losartan were black triangle medicines. An asterisk beside the symbol referred the reader to a list of references which appeared overleaf and which made it clear that the black triangle related to the Cozaar SPC. The Panel noted that the claims could not be qualified by the use of a footnote or the like. The Panel thus considered that the implication that all forms of losartan were black triangle medicines was misleading and in that regard it ruled a breach of Clause 7.2. This ruling was appealed.

The Panel noted that Clause 6.1 required that where the pages of a two page advertisement were not facing, neither must be false or misleading when read in isolation. The Panel noted that the reference to the Cozaar SPC was overleaf from the table of data in question and further noted its comments above about the use of footnotes to qualify claims. However, given its ruling of a breach of Clause 7.2 in relation to page 1 of the advertisement, the Panel did not consider that this meant that it was false or misleading when read in isolation. No breach of Clause 6.1 was ruled. This ruling was not appealed.

Clause 5.7 related to abbreviated advertisements and required companies to display the black triangle when medicines were subject to special reporting in relation to adverse reactions. The advertisement in question was not an abbreviated advertisement and thus Clause 5 did not apply and so no breach of Clause 5.7 was ruled. This ruling was not appealed. A black triangle had been displayed and so the material met the requirements of Clause 4.11 but the Panel made no ruling on this point as the company had not been asked to respond to it either by the complainant or by the Authority.

The Panel noted that prescribing information was an integral part of the advertisement and was included on the second page. No breach of Clause 4.1 was ruled. This ruling was not appealed.

APPEAL BY TAKEDA

Takeda noted that the Panel had noted that generic forms of losartan were now available (from information obtained from www.medicines.org.uk), but that some of these could not be used to initiate treatment in chronic heart failure given that generic tablets of 12.5mg were not available. The Panel acknowledged that the SPCs for these generics did, however, state that they were indicated for chronic heart failure although they did not indicate that they were black triangle medicines.

Takeda noted that the electronic medicines compendium did not contain the SPCs of all generic forms of losartan available in the UK. On review of the MHRA website there were documents relating to marketing authorizations of at least 13 generic forms of losartan 25mg, many of which did not appear on www.medicines.org.uk. Many of the available generic 25mg tablets had a score line that the tablet could be broken in half ie two 12.5mg doses. When a physician prescribed the initiation dose of losartan for heart failure (12.5mg) the prescription would only be filled with a version of losartan that fulfilled this dosing requirement. This could be with either divisible losartan 25mg tablets or 12.5mg tablets. Takeda further noted that the 12.5mg dose was only a titration dose and should only be given for a week. The dose should then be up-titrated to 25mg once daily for a further week and then to the target maintenance dose of 50mg once daily. All generic forms of losartan were available as tablets of 50mg.

Takeda submitted that as stated by the Panel, there did seem to be some confusion regarding this matter. It was absolutely not clear from the MHRA website whether the black triangle applied only to branded versions of an active substance. Furthermore, the SPC for one of the generic losartans (Dexcel Pharma) referred to the intensive monitoring in relation to the heart failure indication (as per the SPC for Cozaar). Takeda never thought to consider that the requirement of the enhanced safety reporting associated with a black triangle did not extend to all forms of an active substance (ie branded and generic versions of a medicine). If it was clear that a black triangle applied only to a branded product then Takeda would not have included it in the advertisement or alternatively the company would have made specific reference to Cozaar only.

Takeda submitted that when the black triangle was introduced, it was intended to cover the first few years following the introduction of a new active substance onto the UK market (ie a period when there would not be any generic versions available). As the black triangle could now be reinstated for medicines which received a significant new indication, there was the possibility (and as was the case with losartan) where a black triangle was still in place when generic versions became available. This was a new situation however and with more and more mature products receiving indications in new patient populations (eg paediatric licence extensions) close to their patient expiry this was going to become a more common occurrence.

Takeda submitted that the final and most fundamental reason for appealing the ruling was patient safety. The purpose of the black triangle in this instance was to ensure enhanced adverse event reporting requirements when losartan was used in patients with heart failure. This was a newly licensed patient population and the purpose of the black triangle was to collect further important safety data when losartan was used in this patient cohort in clinical practice. A health professional should be encouraged to report all adverse events in this population irrespective of which company manufactured the losartan. Generic versions were required to be equivalent medicines in order to obtain a marketing authorization, and for this reason and the fact that they were lower in price, when a branded product lost its patent protection generics become the most widely dispensed form of a medicine. In November 2010, only 4.5% of the total volume of losartan was branded Cozaar and so if only adverse events related to Cozaar were subject to enhanced reporting then the vast majority of patient safety information that would have been reported under these enhanced requirements would go unreported.

Takeda submitted that within clinical practice, a prescriber would not know what form of losartan (Cozaar or a generic) was going to be dispensed at the local pharmacy. Unless the patient brought their tablets with them the physician would not know whether the enhanced safety reporting requirements

applied to any adverse events experienced by that patient. Therefore, the most stringent safety requirements should apply.

For the reasons stated above, Takeda submitted that it was not misleading to include a black triangle next to the 'losartan' in the advertisement at issue. Takeda submitted that if the Panel's ruling of a breach of Clause 7.2 was upheld it would have a significant impact on the effectiveness of the enhanced safety reporting requirements that related to the inclusion of the black triangle symbol, ultimately impacting patient safety.

COMMENTS FROM THE COMPLAINANT

The complainant reiterated that to label generic losartan as a black triangle medicine was, at best, misleading and clearly in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that the first page of the two page advertisement featured a table in which six clinical attributes of the use of candesartan, losartan and valsartan in heart failure were compared. For the most part, ticks were shown for candesartan and crosses for losartan and valsartan. The seventh and final attribute to be compared was 'Black triangle drug' for which candesartan received a cross and losartan and valsartan each received a tick. In the column headings to the table, losartan and valsartan each had a black triangle next to their name. In the Appeal Board's view, Takeda had chosen to highlight the possession, or otherwise, of a black triangle as a means to differentiate the products. The Appeal Board noted that the Code did not require companies to display the black triangle against the names of competitor products. If, however, they chose to do so it must be in a manner which complied with the Code. The Appeal Board considered that the overall aim of the advertisement was to encourage the prescription of Amias, not the reporting of adverse events with losartan or valsartan. By highlighting the black triangle status of the three medicines, prescribers might be inclined to favour candesartan because it was not subject to enhanced surveillance and in that regard might be perceived by some to have patient safety benefits.

The Appeal Board noted that the black triangle status of generic losartan was confusing and appeared illogical given that branded losartan (Cozaar) was subject to enhanced surveillance. The Appeal Board noted Takeda's submission that as the black triangle could now be reinstated for well established medicines which received a new indication, there was a possibility that such reinstatement could still be in place when generic versions became available. Takeda accepted that there was an inconsistency in the labelling of generic losartan. The complainant had pointed out that generic losartan did not carry a black triangle warning in the BNF whereas Cozaar did.

The Appeal Board was concerned about patient safety but considered that its role was to consider the matter in relation to the Code which required information and claims in advertisements to be accurate. Contrary to the impression given by the advertisement at issue not all formulations of losartan were officially designated as black triangle medicines. Although the black triangle next to losartan in the table heading was referenced to the Cozaar SPC, the Appeal Board noted that claims could not be qualified by footnotes and the like. The Appeal Board considered that the advertisement was misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2. The appeal was thus unsuccessful.

During its consideration of the above the Appeal Board expressed some sympathy for Takeda's position and noted the important role that the black triangle played in the maintenance and monitoring of patient safety. Given its concerns in that regard, the Appeal Board requested that the PMCPA inform the MHRA and the ABPI regulatory expert network about the issues raised in this case and ask the MHRA to clarify the position with some urgency.

Complaint received **27 October 2010**

Case completed **6 April 2011**

CASE AUTH/2369/11/10

ABBOTT HEALTHCARE v GENUS

Promotion of APO-go

Abbott Healthcare complained about the promotion of APO-go (apomorphine pen injection system) by Genus. APO-go was indicated for use in patients with Parkinson's disease with disabling motor fluctuations despite treatment with levodopa and/or other dopamine agonists. Abbott Healthcare supplied Duodopa (levodopa/carbidopa) for the treatment of advanced Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia.

The detailed response from Genus is given below.

Abbott Healthcare alleged that the patient booklets Introduction to APO-go Pen and Introduction to APO-go Pump were disguised promotion. Much of the information presented was on the medicine and not the devices as the titles implied and there was prominent use of the brand name and logo.

Genus had argued that the booklets were for patients identified as suitable for APO-go. Abbott Healthcare believed that just because a patient was on a medicine did not mean a company could switch from providing educational information to promotional information without it being disguised promotion.

Despite inter-company dialogue Abbott Healthcare still had issues with the following claims:

- **'APO-go is a highly effective anti-parkinsonian medication'.**

'Highly effective' was a hanging comparison. It was not clear what APO-go was highly effective compared to? Was it oral medication, generic apomorphine etc?

- **'NO! APO-go therapy is not a last option in Pd [Parkinson's disease]; patients can use APO-go Pen therapy in combination with their oral medication or with an APO-go Pump for many years'.**

- **'Nausea doesn't affect everyone, is very temporary'.**

Abbott Healthcare appreciated that adverse events did not affect every patient, however if a product [sic] was listed as common, ie might affect less than one in every 100 patients, and domperidone had to be used at initiation of therapy it was misrepresentative to state such a claim especially when the audience were patients not health professionals.

- **'Nodule formation is usually not a significant problem'.**

Not consistent with summary of product characteristics (SPC).

Abbott Healthcare alleged that the booklets failed to meet high standards, lacked safety data, side effect profile and contraindications etc which could prejudice patient safety and therefore brought discredit to the industry (breach of Clause 2).

The Panel noted that Genus had not categorically stated what the target audience was for the booklets. The company had variously stated that they were for those identified as 'being APO-go patients' and for those identified as 'being suitable for APO-go therapy'. It was thus unclear as to whether the booklets were intended for those already receiving APO-go therapy or for those considering starting such therapy. The Panel examined the content of the booklets and noted that the pen booklet referred to patients who were already using the APO-go pump but needed a boost at various times of the day. Both booklets, however, 'introduced' patients to APO-go and listed the benefits of therapy and gave detailed information about the challenge test. In the Panel's view the booklets were most likely to be given to patients who were being considered for APO-go therapy but for whom the prescribing decision could not be made until the results of the challenge test were known. In the Panel's view the booklets were designed to influence a patient's decision as to whether to start APO-go therapy should the challenge test be successful.

The Panel considered that companies could prepare material about a product for patients who might be prescribed that product but it was very important that such material met all the relevant requirements of the Code. The Code prohibited the promotion of a prescription only medicine to the public. It permitted the provision of factual information presented in a balanced way. Such material must not raise unfounded hopes of successful treatment or be misleading about the safety of a product. In addition, the Code required that statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a prescription only medicine.

In relation to the Introduction to APO-go Pen booklet, the Panel did not consider that the claim that 'APO-go is a highly effective anti-parkinsonism medication' was a hanging comparison as alleged. No comparison was made or implied and thus the Panel ruled no breach.

The Panel noted the vague allegation with regard to the claim 'No! APO-go therapy is not the last

option in Pd; patients can use APO-go Pen therapy in combination with their oral medication or with an APO-go Pump for many years'. The Panel did not consider that the claim in itself constituted advertising a prescription medicine to the public. It was factual and balanced. The Panel did not consider that the complainant had proven this allegation on the balance of probabilities and thus ruled no breach.

The Panel noted that under the heading 'What are the possible side effects of APO-go Pen therapy' it was stated that 'APO-go Pen can cause nausea and vomiting as well as low blood pressure. Nausea doesn't affect everyone, is very temporary and usually only occurs when APO-go Pen therapy is first initiated. Domperidone (Motilium), an anti-sickness medication, is always used with APO-go initiation to avoid nausea'. The APO-go pen SPC stated that patients must be established on domperidone for at least two days prior to initiation of therapy. Once treatment had been established domperidone therapy might be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension. The Panel thus did not consider that with regard to the incidence and duration of nausea, the booklet fairly reflected the information in the SPC and was misleading in that regard. Breaches of the Code were ruled.

The Panel noted that under the same heading it was stated that 'Nodule formation occurs in some APO-go patients' and was 'usually not a significant problem, but occasionally if severe, can lead to erratic absorption of the drug and may affect the therapeutic outcome'. The APO-go pen SPC stated that most patients experienced injection site reactions, particularly with continuous use, including subcutaneous nodules. The Panel thus did not consider that to state that nodule formation only occurred in some patients accurately reflected the data in the SPC and was thus misleading in that regard. Breaches of the Code were ruled.

In relation to the Introduction to APO-go Pump booklet, the Panel considered that its last three rulings above applied. Its ruling about the claim 'APO-go is a highly effective anti-parkinsonian medication …' did not apply as this claim did not appear in the Introduction to APO-go Pump booklet.

The Panel considered that both booklets would influence patients regarding APO-go therapy. On balance the Panel considered that the booklets constituted advertising a prescription only medicine to the public and a breach of the Code was ruled. The Panel noted that the introduction to both booklets stated that APO-go had '… a similar effect to the gold standard treatment, levodopa'. The Panel considered that to describe a medicine as a model of excellence did not meet the requirements of the Code; information about APO-go had not been presented in a balanced way. It also noted its rulings of breaches above which it considered meant that the booklets were not factual and were misleading. A breach of the Code was ruled.

The Panel considered that as promotion of a prescription only medicine to the public was not allowed such promotion could not be disguised. No breach was ruled in that regard.

The Panel did not consider that the content of the booklets was misleading given their titles. They both contained information relevant to the medicine and its method of administration. The booklets were not comprehensive in relation to side effects. Only nausea and skin nodules were mentioned. There were other side effects listed in the SPC that were not included in the section headed 'What are the possible side effects of APO-go [Pen/continuous infusion] therapy?'. This was not balanced and was misleading with respect to the safety of the medicine. Breaches of the Code were ruled. The use of the brand name was not misleading. No breach was ruled in that regard.

The Panel did not consider that high standards had been maintained and a breach was ruled. The Panel did not consider that the circumstances warranted a ruling of Clause 2 which was used as a particular sign of censure and reserved for such use.

In relation to the Skin Management Guide, Abbott Healthcare stated that this patient literature was still available despite issues raised regarding Code breaches. In particular, Abbott Healthcare had issue with a claim that skin nodules were more likely to be caused with poor skin care.

The SPC stated 'most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis'. These were listed as very common ie less than one in ten patients. This was not reflected in this leaflet.

The Panel noted that the document at issue was a four page, A4 leaflet entitled 'APO-go skin management'. The first paragraph, headed 'What are skin nodules?', explained that a side effect of APO-go therapy could be redness, tenderness, itching and the development of nodules and/or hardening of the skin at the injection site. A section 'What causes them?' followed and referred to a local inflammatory reaction which varied greatly between individuals and which '… sometimes occurs in response to the medication or the needle and is more likely with poor skin care'. The next two pages headed 'What can I/my carer do to help minimise or prevent these skin reactions?' included information regarding hygiene, choosing an injection site and needle siting. The final page referred to treatment of existing nodules/hardened skin areas and included the statement that 'skin nodules although common, present no significant problems in the majority and shouldn't stop treatment'.

The SPC stated general disorders and administrative site conditions were very common

(≥1/10). Most patients experienced injection site reactions particularly with continuous use. These might include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) might also occur.

The Panel considered that the purpose of the leaflet in question was to explain to patients what skin nodules were, how they were caused, encourage patients and carers to follow good hygiene practices, to give advice about siting needles etc and to explain what could be done if skin nodules developed. The Panel considered that the leaflet was clear that APO-go therapy was associated with the development of skin nodules in response to the medication or to the needle and was more likely with poor skin care. The Panel considered that Abbott Healthcare's allegation was vague; no details had been provided as to why the claim was alleged to be in breach of the Code. The Panel thus did not consider that Abbott Healthcare had proven its complaint on the balance of probabilities. The Panel did not consider that the booklet was misleading about the cause of skin nodules as alleged. It did not state that these were wholly due to poor skin hygiene. No breach of the Code was ruled in this regard.

The Panel considered that the booklet was misleading about the incidence of injection site reactions. The leaflet stated that skin nodules were common whereas the SPC stated that injection site reactions were very common and experienced by most patients. A breach of the Code was ruled.

Abbott Healthcare Products Ltd complained about the promotion of APO-go (apomorphine pen injection system) by Genus Pharmaceuticals Ltd. APO-go was indicated for use in patients with Parkinson's disease with disabling motor fluctuations despite treatment with levodopa and/or other dopamine agonists. Inter-company dialogue had left certain matters unresolved. Abbott Healthcare supplied Duodopa (levodopa/carbidopa) for the treatment of advanced Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia.

1 Introduction to APO-go Pen (APO-0210-669) and Introduction to APO-go Pump (APO-0110-640) patient booklets

COMPLAINT

Abbott Healthcare alleged that the booklets were disguised promotion. Much of the information presented was on the medicine and not the devices as the titles implied, in breach of Clause 7.2, and there was prominent use of the brand name and logo.

Genus had argued that the booklets were for patients identified as suitable for APO-go. Abbott Healthcare believed that just because a patient was on a medicine did not mean a company could switch from providing educational information to promotional information without it being disguised promotion.

Despite inter-company dialogue Abbott Healthcare still had issues with the following claims:

- 'APO-go is a highly effective anti-parkinsonian medication'. (Breach of Clause 7.2).

  'Highly effective' was a hanging comparison. It was not clear what APO-go was highly effective compared to? Was it oral medication, generic apomorphine etc?

- 'NO! APO-go therapy is not a last option in Pd [Parkinson's disease]; patients can use APO-go Pen therapy in combination with their oral medication or with an APO-go Pump for many years'. (Breach of Clause 22).

- 'Nausea doesn't affect everyone, is very temporary'. (Breach of Clauses 7.2 and 7.9).

  Abbott Healthcare appreciated that adverse events did not affect every patient, however if a product [sic] was listed as common ie might affect less than one in every 100 patients and domperidone had to be used at initiation of therapy it was misrepresentative to state such a claim especially when the audience were patients not health professionals.

- 'Nodule formation is usually not a significant problem'. (Breach of Clauses 7.2 and 7.9).

  Not consistent with summary of product characteristics (SPC).

Although the booklets were for patients identified as suitable for APO-go, claims must not be written with promotional intent. Abbott Healthcare believed that the booklets failed to meet the high standards set by the industry (breach of Clause 9.1), lacked safety data, side effect profile and contraindications etc (breach of Clause 7.9) which could prejudice patient safety and therefore brought discredit to the industry (breach of Clause 2).

Abbott Healthcare alleged breaches of Clauses 2, 7.2, 7.9, 9.1, 12.1 and 22 and asked that the booklets and claims at issue be withdrawn.

RESPONSE

Genus did not consider that the booklets were in breach of the Code; they were not for the public, they were for those identified as being APO-go patients. The booklets informed patients about the medicine their health professional had recommended and so encouraged concordance, and thus tied in with the recent NHS White Paper theme of informed patients and 'no decision about me, without me'.

With regard to Abbott Healthcare's ongoing

misunderstanding around the 'device vs drug' issue, Genus had explained several times that due to the unique nature of APO-go and the fact that it was administered subcutaneously, referring to the pen and pump was entirely acceptable as they were each integral to the product.

The APO-go pen was a registered medicinal product.

The APO-go pump referred to the continuous infusion, and the medicine and device were fundamentally linked: neither could be used alone. Genus' branded pump could only be used with the peripherals that were supplied with the pre-filled syringe or APO-go ampoules.

Therefore, Genus did not believe that the booklets were disguised promotion, or that it had 'switched' from providing educational information. The booklets were entirely clear.

In relation to the four claims at issue, Genus stated that its response was the same as previously submitted to Abbott Healthcare.

- 'Highly effective'. This claim was factual, did not use any superlatives and was not 'disguised promotion' as these pieces were for patients already identified as APO-go patients. This was not a hanging comparison as it was not stated that APO-go was highly effective compared with anything. Several products could be highly effective in the same context.

- 'NO! APO-go is not a last option ...'. The booklets were for patients identified as suitable for APO-go, and this claim, which was fact (the National Institute for Health and Clinical Excellence (NICE) Guidelines algorithm was provided) was to reassure patients that by having APO-go therapy they had not exhausted their Parkinson's disease management options. The claim that patients could be on APO-go for many years was also factual, and so Genus did not believe there was an issue with this claim. This provided balanced and fair information to help educate. There was no need, or intention, to promote as these patients had already been chosen for APO-go. Again, this coincided with the 2010 NHS White Paper surrounding informed patients, and Genus did not consider there was a breach of the Code.

- 'Nausea doesn't affect everyone ...'. Genus submitted that this claim, in context of the full paragraph from which it had been taken, was not misrepresentative. The preceding sentence and following details put the claim in a clear context: 'APO-go [PEN/continuous infusion] can cause nausea and vomiting as well as low blood pressure. Nausea doesn't affect everyone, is very temporary and usually only occurs when APO-go [PEN/continuous infusion] therapy is first initiated. Domperidone (Motilium), an anti-sickness medication, is always used with APO-go initiation to avoid nausea.' Therefore, Genus submitted this was an accurate declaration. Not all patients were affected by nausea, especially those who had already been on dopaminergic therapies. The use of domperidone was a prophylactic measure as it was not known which patients would be affected, and so represented good clinical practice. Genus did not agree this was in breach of Clause 7.9 as the statement reflected available evidence and was capable of substantiation by clinical experience.

- 'Nodule formation is usually not a significant problem'. Genus submitted that the context in which the above claim appeared in both booklets was balanced and fair: 'Nodule formation occurs in some APO-go patients. Although apomorphine is rapidly absorbed from subcutaneous tissue, in some instances when the muscle underneath isn't active enough, it can pool in the skin causing nodules to form. Nodule formation is usually not a significant problem, but occasionally, if severe, can lead to erratic absorption of the drug and may affect the therapeutic outcome. Any nodule formation can be improved with strict rotation of the injection site used and improved skin hygiene'. Genus stated 'not usually a significant problem' and by doing so conceded that there was a problem, but one that could be managed. In context this was perfectly balanced and was based on available evidence and clinical experience. Genus (formerly Britannia) had almost 20 years' experience in Parkinson's management with APO-go.

PANEL RULING

The Panel noted that Genus had not categorically stated what the target audience was for the booklets. The company had variously stated that they were for those identified as 'being APO-go patients' and for those identified as 'being suitable for APO-go therapy'. It was thus unclear as to whether the booklets were intended for those already receiving APO-go therapy or for those considering starting such therapy. The Panel examined the content of the booklets and noted that the pen booklet referred at one point to patients who were already using the APO-go pump but needed a boost at various times of the day. Both booklets, however, 'introduced' patients to APO-go and listed the benefits of therapy and a quarter of each book (2 to 3 pages) gave detailed information about the challenge test. In the Panel's view the booklets were most likely to be given to patients who were being considered for APO-go therapy but for whom the prescribing decision could not be made until the results of the challenge test were known. In the Panel's view the booklets were designed to influence a patient's decision as to whether to start APO-go therapy should the

challenge test be successful.

The Panel considered that companies could prepare material about a product for patients who might be prescribed that product but it was very important that such material met all the relevant requirements of the Code, particularly Clauses 22.1 and 22.2. Clause 22.1 prohibited the promotion of a prescription only medicine to the public. Clause 22.2 permitted the provision of factual information presented in a balanced way to the public either directly or indirectly. Such material must not raise unfounded hopes of successful treatment or be misleading about the safety of a product. In addition, Clause 22.2 required that statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a prescription only medicine.

Introduction to APO-go Pen booklet

The Panel did not consider that the claim that 'APO-go is a highly effective anti-parkinsonism medication' on page 2, was a hanging comparison as alleged. No comparison was made or implied and thus the Panel ruled no breach of Clause 7.2.

The Panel noted the vague allegation of a breach of Clause 22 with regard to the claim 'No! APO-go therapy is not the last option in Pd; patients can use APO-go Pen therapy in combination with their oral medication or with an APO-go Pump for many years' on page 6. The Panel did not consider that the claim in itself constituted advertising a prescription medicine to the public as prohibited by Clause 22.1. Nor did it fail to meet the requirements of Clause 22.2. It was factual and balanced. The Panel did not consider that the complainant had proven this allegation on the balance of probabilities and thus with regard to this specific claim ruled no breach of Clause 22.

The Panel noted that under the heading 'What are the possible side effects of APO-go Pen therapy' it was stated that 'APO-go Pen can cause nausea and vomiting as well as low blood pressure. Nausea doesn't affect everyone, is very temporary and usually only occurs when APO-go Pen therapy is first initiated. Domperidone (Motilium), an anti-sickness medication, is always used with APO-go initiation to avoid nausea'. The APO-go pen SPC stated that patients must be established on domperidone for at least two days prior to initiation of therapy. Once treatment had been established domperidone therapy might be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension. The Panel thus did not consider that with regard to the incidence and duration of nausea, the booklet fairly reflected the information in the SPC and was misleading in that regard. Breaches of Clauses 7.2 and 7.9 were ruled.

The Panel noted that under the same heading it was stated that 'Nodule formation occurs in some APO-go patients' and was 'usually not a significant problem, but occasionally if severe, can lead to erratic absorption of the drug and may affect the therapeutic outcome'. The APO-go pen SPC stated that most patients experienced injection site reactions, particularly with continuous use, including subcutaneous nodules. The Panel thus did not consider that to state that nodule formation only occurred in some patients accurately reflected the data in the SPC and was thus misleading in that regard. Breaches of Clauses 7.2 and 7.9 were ruled.

Introduction to APO-go Pump booklet

The Panel considered that its last three rulings above applied to the Introduction to APO-go Pump booklet. Its ruling about the claim 'APO-go is a highly effective anti-parkinsonian medication …' did not apply as this claim did not appear in the Introduction to APO-go Pump booklet.

Both booklets

The Panel noted the general allegation of a breach of Clause 22. It first considered the requirements of Clause 22.1. The Panel considered that the booklets would influence patients regarding APO-go therapy. On balance the Panel considered that the booklets constituted advertising a prescription only medicine to the public and a breach of Clause 22.1 was ruled. Turning now to Clause 22.2, the Panel noted that the introduction to both booklets stated that APO-go had '… a similar effect to the gold standard treatment, levodopa'. The Panel considered that to describe a medicine as a model of excellence did not meet the requirements of Clause 22.2; information about APO-go had not been presented in a balanced way. It also noted its rulings of breaches above which it considered meant that the booklets were not factual and were misleading. A breach of Clause 22.2 was ruled.

With regard to the alleged breach of Clause 12.1, the Panel considered that as promotion of a prescription only medicine to the public was not allowed such promotion could not be disguised. No breach of Clause 12.1 was ruled. The matter at issue was better dealt with under Clause 22 of the Code.

The Panel did not consider that the content of the booklets was misleading given their titles. They both contained information relevant to the medicine and its method of administration. The booklets were not comprehensive in relation to side effects. Only nausea and skin nodules were mentioned. There were other side effects listed in the SPC that were not included in the section headed 'What are the possible side effects of APO-go [Pen/continuous infusion] therapy?'. This was not balanced and was misleading with respect to the safety of the medicine. Breaches of Clauses 7.2 and 7.9 were ruled. The use of the brand name was not misleading. No breach of Clause 7.2 was ruled.

The Panel did not consider that high standards had been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of Clause 2 which

was used as a particular sign of censure and reserved for such use.

2 Skin management guide (APO-0110-654)

COMPLAINT

Abbott Healthcare stated that this patient literature was still available despite issues raised regarding Code breaches. In particular, Abbott Healthcare had issue with a claim that skin nodules were more likely to be caused with poor skin care. (Breach of Clause 7.9).

The SPC stated 'most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis'. These were listed as very common ie less than one in ten patients. This was not reflected in this leaflet.

Clause in breach: 7.9.

RESPONSE

Genus noted that Clause 7.9 stated that 'Information and claims about side-effects must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product has no side-effects, toxic hazards or risks of addiction or dependence. The word "safe" must not be used without qualification'. Genus denied that the claim at issue was in breach of Clause 7.9 and submitted that it reflected available evidence, such as Todd *et al* (2008) which listed hygiene as the top key consideration for siting infusions and for best practice to prevent and manage nodule formation. Genus also referred to a 2010 BMJ insert 'Role of apomorphine in the management of Parkinson's disease' which stated that nodules could be minimised by more frequent change of infusion needles, attention to hygiene upon needle insertion and local ultrasound physiotherapy.

PANEL RULING

The Panel noted that the document at issue was a four page, A4 leaflet entitled 'APO-go skin management'. The first paragraph, headed 'What are skin nodules?', explained that a side effect of APO-go therapy could be redness, tenderness, itching and the development of nodules and/or hardening of the skin at the injection site. A section 'What causes them?' followed and referred to a local inflammatory reaction which varied greatly between individuals and which '… sometimes occurs in response to the medication or the needle and is more likely with poor skin care'. The next two pages headed 'What can I/my carer do to help minimise or prevent these skin reactions?' included information regarding hygiene, choosing an injection site and needle siting. The final page referred to treatment of existing nodules/hardened skin areas and included the statement that 'skin nodules although common, present no significant problems in the majority and shouldn't stop treatment'.

The SPC stated general disorders and administrative site conditions were very common (≥1/10). Most patients experienced injection site reactions particularly with continuous use. These might include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) might also occur.

The Panel considered that the purpose of the leaflet in question was to explain to patients what skin nodules were, how they were caused, encourage patients and carers to follow good hygiene practices, to give advice about siting needles etc and to explain what could be done if skin nodules developed. The Panel considered that the leaflet was clear that APO-go therapy was associated with the development of skin nodules in response to the medication or to the needle and was more likely with poor skin care. The Panel considered that Abbott Healthcare's allegation was vague; no details had been provided as to why the claim was alleged to be in breach of the Code. The Panel thus did not consider that Abbott Healthcare had proven its complaint on the balance of probabilities. The Panel did not consider that the booklet was misleading about the cause of skin nodules as alleged. It did not state that these were wholly due to poor skin hygiene. No breach of Clause 7.9 was ruled in this regard.

The Panel considered that the booklet was misleading about the incidence of injection site reactions. The leaflet stated that skin nodules were common whereas the SPC stated that injection site reactions were very common and experienced by most patients. A breach of Clause 7.9 was ruled.

Complaint received **11 November 2010**

Case completed **14 March 2011**

ANONYMOUS EMPLOYEE v SANOFI-AVENTIS

Alleged excessive hospitality

An anonymous employee of Sanofi-Aventis alleged that the company had provided excessive hospitality to delegates at two overseas meetings. At the first meeting, held in Paris in 2009, it was alleged that Sanofi-Aventis plied customers with large amounts of alcohol and that individual entertainment bills ranged from £200 to in excess of £500. The complainant further alleged that at a second meeting in San Francisco one named individual was wined and dined excessively; on one occasion the cost was over $100 per head for entertainment only. The complainant alleged that the excessive entertainment/alcohol provided to the named individual led him to behave inappropriately in the bar.

For each meeting the complainant named a number of employees who, to his recollection, had attended.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that the complainant had not revealed their identity nor given the Authority any contact details. Complainants had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints were judged on the evidence provided by the parties. With no contact details for the complainant it was impossible to ask him/her for further information.

The Panel was concerned that Sanofi-Aventis had not spoken to the company employees who had attended the meetings. The company had referred solely to its records. With regard to the Paris meeting the Panel noted that on the two evenings a three course meal with wine was provided to delegates at a cost of around £55. The complainant had not complained about this hospitality *per se*; his complaint was about the employees' bills for entertaining customers. Nonetheless, the Panel considered that what the company had already provided by way of hospitality was an important factor in deciding whether any additional spend was acceptable under the Code.

Sanofi-Aventis had provided copies of three employees' room bills which in total related to 46 delegates and 11 employees. A bar bill from a fourth employee (for 4 delegates) stated a time of 18.35 and itemised the drinks, three gin and tonics, what appeared to be a beer and a coffee. The room bills did not break down the drinks, the number of drinks or the number of attendees or give the time of day.

The Panel noted from the information provided that drinks over two days for 50 delegates and 11 employees had cost £1568.41 with an average spend of £25.71. The bar bill for day one was £1030.30 and day two £538.11. Sanofi-Aventis was unable to say how many delegates, staff or agency employees were present in the bar each evening or what had been drunk and had not stated whether the drinks were consumed before or after dinner. In the Panel's view there was a difference in perception between providing one drink prior to dinner and post dinner drinks.

The Panel was extremely concerned about the lack of information regarding expenses for the Paris meeting. It had asked Sanofi-Aventis for additional information and this had not been supplied. The Panel noted that Sanofi-Aventis' record of the events was extremely limited. If, in 2009, the company had had no more information than it provided to the Panel in 2010/11, it appeared to have approved expenses with incomplete information. If this was the case then in the Panel's view this was extremely poor practice.

The Panel noted that given the lack of detail provided by Sanofi-Aventis it did not know the nature of the hospitality nor could it calculate the exact level of hospitality provided to delegates on either evening; it could only calculate the average figures. In the Panel's view this was unsatisfactory and it meant that the true level of hospitality provided to some individuals might be higher but hidden in the average figure. Sanofi-Aventis could not guarantee that the requirements of the Code had been met. The Panel queried whether the bar costs exceeded the level which recipients would normally adopt when paying for themselves. The Panel considered that based on the limited evidence before it, it had no option other than to rule no breach of the Code including no breach of Clause 2 which was a sign of censure and reserved for such.

With regard to the American meeting the Panel noted that the complaint appeared to be about both the hospitality provided by the company and the hospitality provided by the employees. Sanofi-Aventis had submitted that in addition to providing delegates with a £36.53 hotel voucher for the first evening, it had organised two evening meals which had cost £60.54 and £45.39 per head on the second and fourth evenings respectively. Each meal had been a three course dinner with a half bottle of wine, coffee/tea and water, local taxes and gratuities. On the third evening delegates had attended a symposium dinner the cost of which was included in the registration package. No company employee submitted any additional expense claim for any third party entertainment.

The Panel considered that on the information before it there was no evidence that the hospitality was unreasonable. No breach of the Code was ruled including no breach of Clause 2.

The Panel was extremely concerned that the complainant had made some very serious allegations about the hospitality provided to, and the conduct of, a named consultant. No supporting evidence was provided by the complainant. There was no evidence that Sanofi-Aventis had provided hospitality other than dinner and drinks. The Panel ruled no breach of the Code.

An anonymous Sanofi-Aventis employee complained about hospitality provided by the company at meetings in Paris and San Francisco.

COMPLAINT

The complainant stated that after working for Sanofi-Aventis for a considerable number of years he now sadly found himself in a position to be able to report a number of clear breaches of the Code without fear of retribution as he was possibly facing redundancy.

International Breast Cancer Conference (IBCC)

The complainant explained that the IBCC was an annual meeting held each year in Paris and organised by Sanofi-Aventis. The meeting in question had been held in January 2009 and was attended by delegates from Europe and further afield. Company employees were given specific instructions before they left for the meeting around the Code and entertaining customers. Specifically, that all meals and refreshments were provided and that there would be absolutely no need for them to incur any cost relating to entertainment of customers.

At this meeting Sanofi-Aventis employees plied customers with large amounts of alcohol which was at the time clearly in breach of the Code. It was a two night stay and the individual entertainment bill ranged from £200 to in excess of £500. There were at least six employees present. The meeting would be held again in 2011.

The complainant named ten company employees who, to his recollection, had attended the meeting.

American Society of Clinical Oncology – Genitourinary Meeting (ASCO GU)

The complainant alleged that during ASCO GU 2010, held in San Francisco, several incidents took place that were an utter shame on his profession. Sanofi-Aventis breached the Code on at least two separate occasions. Firstly with the entertainment of a named UK consultant oncologist, who was wined and dined excessively; on one occasion the cost was over $100 per head which was purely entertainment.

The amount of excessive entertainment/alcohol this oncologist received on another occasion at this event in the presence of Sanofi-Aventis employees led him to behave inappropriately in the bar.

The complainant named eight company employees who, to his recollection, had attended the meeting.

The complainant stated that the practice had to stop.

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Sanofi-Aventis stated that the IBCC was an annual Sanofi-Aventis organised three day meeting held in Paris, where oncologists across the globe were invited to listen to the latest research and treatment of breast cancer from an international panel of experts. Sanofi-Aventis UK sponsored 98 delegates, 14 company and 2 agency employees to attend the meeting in 2009. As outlined by the complainant, a comprehensive verbal staff briefing was provided to Sanofi-Aventis employees attending this meeting; in particular Clause 19.1 was outlined.

The sponsorship of each delegate included travel, accommodation, registration to the conference and hospitality. The hospitality consisted of breakfasts, lunches provided at the conference and, furthermore, the whole UK team was invited for pre-arranged dinner each night, as outlined below:

First Night: $60.13 per head for a 3 course set dinner including 1/3 bottle of wine, mineral water, coffee, including local taxes and gratuities.

Second Night: $60.70 per head for a 3 course dinner including 1/2 bottle of wine, mineral water, coffee, including local taxes and gratuities.

In addition to the above, four company representatives had claimed for third party entertainment over the two nights in Paris: 83.00 Euros for 4 delegates; 737.00 Euros for 26 delegates; 616.00 Euros for 13 delegates and 6 employees and 272.00 Euros for 7 delegates and 5 employees respectively.

For reference, the average cost of drinks at the hotel bar was beer €12-14 (£11-12.86), gin & tonic €18 (£16.53) and glass of wine €8 (£7.35). No out of pocket expenses referring to hospitality were claimed by any of the delegates attending this meeting.

ASCO GU was an annual international cancer conference held in the US specifically to deliver the latest research and treatment paradigms in genitourinary oncology. Sanofi-Aventis UK sponsored 56 delegates, 8 employees and 2 agency employees to attend the meeting in 2010. A staff briefing was provided to Sanofi-Aventis employees attending this meeting; in particular Clause 19.1 was outlined.

The sponsorship of each delegate included travel, accommodation, registration to the conference and hospitality. The hospitality consisted of breakfasts, lunches provided at the conference and, the whole UK team was invited for pre-arranged dinner each night, as outlined below:

3 March - Hotel voucher

4 and 6 March - Local restaurants: $82.85 and $62.12 per head respectively for a 3 course dinner including a half bottle of wine, tea/coffee, water, local taxes and gratuities.

5 March - Congress symposium included dinner

Sanofi-Aventis stated that none of its employees submitted expense claims for any third party entertainment during their stay in San Francisco. Furthermore, no out of pocket expenses referring to hospitality were claimed by any of the delegates.

Sanofi-Aventis took the matter of providing an appropriate and acceptable level of hospitality at all meetings very seriously and it did not believe that on either occasion the allegations of inappropriate hospitality, and therefore a breach of Clause 19.1, could be justified. Furthermore, the company believed that the briefings and arrangements as outlined above were in keeping with the requirements to maintain high standards at all times. Sanofi-Aventis therefore denied breaches of Clauses 9.1 and 2.

Sanofi-Aventis noted that its whistle-blowing policy encouraged and provided an opportunity for employees to raise concerns such as that described by the complainant. This was not done in this case.

In response to a request for further information, Sanofi-Aventis stressed that its internal records related to these conferences had been thoroughly reviewed and the relevant data summarised above. No staff members that had attended the meetings had been interviewed in relation to this complaint.

With regard to the IBCC in Paris in 2009, Sanofi-Aventis provided copies of the receipts for the additional expenses incurred by the four company representatives, with costs in Sterling, as requested.

With regard to the ASCO GU meeting in San Francisco in 2010, although Sanofi-Aventis considered that it was inappropriate to comment on individual health professionals without their consent, all delegates received the same hospitality and none of them were wined, dined and entertained to excess.

In response to a second request for further information Sanofi Aventis stated that, in relation to the IBCC meeting it was unable to say how many delegates, Sanofi-Aventis staff and agency staff were present in the bar on any of the evenings in question. Furthermore, it did not have any further information on what actual drinks were consumed; it previously supplied all the information which was from the expense claims. Sanofi-Aventis did not pay for any delegate hospitality provided by employees of its agency.

Sanofi-Aventis submitted that it was difficult to comment specifically on what the complainant stated that he was told. All company personnel present at the meeting would have been expected to be conversant with the Code and thus be aware of the costs they could incur.

With regard to the ASCO GU meeting, the exchange rate at that time was 1.3686. The hotel voucher was for $50 inclusive of taxes and gratuities for a delegate to use in any of the hotel restaurants. Any expenses over this were paid by the delegates themselves. The conference dinner on 5 March was included in the cost of the registration package and was not paid as an extra. Again Sanofi-Aventis did not pay any delegate hospitality provided by employees of its agency.

PANEL RULING

The Panel noted that the complainant had not revealed their identity nor given the Authority any contact details. 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 were judged on the evidence provided by the parties. With no contact details for the complainant it was impossible to ask him/her for further information.

The Panel was concerned that Sanofi-Aventis had not spoken to the company employees who had attended the meetings. The company had referred solely to its records. With regard to the IBCC meeting the Panel noted that on the two evenings a three course meal with wine was provided to delegates at a cost of €60.13 (£55.22) and €60.70 (£55.74) respectively. The complainant had not complained about this hospitality *per se*; his complaint was about the employees' bills for entertaining customers. Nonetheless, the Panel considered that what the company had already provided by way of hospitality was an important factor in deciding whether any additional spend was acceptable under the Code.

The documents provided by Sanofi-Aventis consisted of copies of the room bills for three employees and a copy of a bar bill from a fourth. The copy of the bar bill (for 4 delegates) stated a time of 18.35 and itemised the drinks, three gin and tonics, what appeared to be a beer and a coffee. The other three bills (for a total of 46 delegates and 11 employees) did not break down the drinks, the number of drinks or the number of attendees or give the time of day.

The Panel noted from the information provided that drinks over two days for 50 delegates and 11 employees had cost €1,708 (£1568.41) with an average spend of €28 (£25.71). The bar bill for day one was €1,122 (£1030.30) and day two €586

(£538.11). In a further submission Sanofi-Aventis stated that it was unable to say how many delegates, staff or agency employees were present in the bar each evening or what had been drunk. The Panel noted that Sanofi-Aventis had not answered its enquiry as to whether the drinks were consumed before or after dinner. In the Panel's view there was a difference in perception between providing one drink prior to dinner and post dinner drinks.

The Panel was extremely concerned about the lack of information regarding expenses for the IBCC meeting. It had asked Sanofi-Aventis for additional information and this had not been supplied. The Panel noted that Sanofi-Aventis' record of the events was extremely limited. If, in 2009, the company had had no more information than it provided to the Panel in 2010/11, it appeared to have approved expenses with incomplete information. If this was the case then in the Panel's view this was extremely poor practice.

The Panel noted that given the lack of detail provided by Sanofi-Aventis it did not know the nature of the hospitality nor could it calculate the exact level of hospitality provided to delegates on either evening; it could only calculate the average figures. In the Panel's view this was unsatisfactory as it meant that the true level of hospitality provided to some individuals might be higher but hidden in the average figure. Sanofi-Aventis could not guarantee that the requirements of the Code had been met. The Panel queried whether the bar costs exceeded the level which recipients would normally adopt when paying for themselves. The Panel considered that based on the limited evidence before it, it had no option other than to rule no breach of Clause 19.1. It did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of censure and reserved for such.

With regard to the ASCO meeting the Panel noted that the complaint appeared to be about both the hospitality provided by the company and the hospitality provided by the employees. Sanofi-Aventis had submitted that in addition to providing delegates with a $50 (£36.53) hotel voucher for the first evening, it had also organised two evening meals which had cost $82.85 (£60.54) and $62.12 (£45.39) per head on the second and fourth evenings respectively. Each meal had been a three course dinner with a half bottle of wine, coffee/tea and water, local taxes and gratuities. On the third evening delegates had attended a symposium dinner the cost of which was included in the registration package. No company employee submitted any additional expense claim for any third party entertainment.

The Panel considered that on the information before it there was no evidence that the hospitality was unreasonable such as to breach Clause 19.1. Thus the Panel ruled no breach of that clause. It also ruled no breach of Clauses 2 and 9.1.

The Panel was extremely concerned that the complainant had made some very serious allegations about the hospitality provided to, and the conduct of, a named consultant. No supporting evidence was provided by the complainant. There was no evidence that Sanofi-Aventis had provided hospitality other than dinner and drinks. The Panel ruled no breach of Clause 19.1. Given the circumstances, the Panel also ruled no breach of Clauses 2 and 9.1.

Complaint received **22 November 2010**

Case completed **7 February 2011**

FORMER EMPLOYEE v ASTELLAS

Promotional practices

A former employee of Astellas Pharma complained about the company's promotional practices and alleged that the number of breaches and their severity, brought the industry into disrepute and abused the limited public funds provided to the NHS. The complainant provided a copy of a letter which he had sent to two NHS chief executives detailing the breaches and stated that majority of the points discussed fell under Clause 2 of the Code. These being inducement to prescribe to doctors to switch patients' from generic medicines to Astellas brands, prejudicing patient safety, misleading promotional/activities in relation to meetings and misleading sales activities by encouraging over-prescription of Zineryt.

Various promotional meetings had invitations with letters attached with an NHS logo requesting the attendance of the GP. The meeting was sold as an NHS meeting, yet was a promotional activity for the company. Delegates all complained afterwards that the meeting was a disguised promotional activity and that the use of NHS logos was misleading and caused offence. The complainant stated that his manager asked him to confirm that attendees had received their 'NHS urology meeting invitation', and inform them that attendance was mandatory. All delegates received large branded 'goody' bags. Attendance certificates were used as 'access tools' to follow up all the promotional messages delivered at the meeting.

During a promotional call with a dispensing GP, the commercial discounts were also calculated for the surgery. This was a breach of the Code. Once the profits had been calculated for the surgery, GPs were then advised that Astellas could either offer an intervention service to switch all patients from generic products onto branded products, or offer the GP excessive payment to cover the time they would need to do the switch themselves. This was a direct inducement to prescribe the company's products. This activity was evidenced in the field visit report carried out by the complainant's manager, who trained him to carry out the call like this. Following on from the call the complainant was congratulated and rewarded for securing a switch program.

The detailed response from Astellas Pharma is given below.

The Panel noted that the complainant had made a number of serious allegations including some about the conduct of his manager. Astellas denied all the allegations. It appeared that much of this case related to one person's word against another. It was difficult in such cases to determine where the truth lay. As stated in the introduction to the Constitution and Procedure a complainant had the burden of proving their complaint on the balance of probabilities. The complainant had provided very little material to support his position. A judgement had to be made on the available evidence.

The Panel noted that more detail about the allegations was included in the letter the complainant sent to the NHS chief executives. The complainant had called upon dispensing doctors and considered that the Code required discussions about discounts to be separated from the promotion of those medicines' clinical benefits. This was not necessarily so. Such activities were promotional and the Panel considered that, provided that the requirements of the Code were otherwise met clinical and commercial discussions could occur in the same call. It appeared that the complainant's manager preferred his representatives to discuss the two topics in separate calls which might be prudent but it was not a breach the Code *per se* to do otherwise. No detailed allegations had been made. The Panel ruled no breach of the Code.

The supplementary information to the Code, Terms of Trade, stated that measures or trade practices relating *inter alia* to discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 were outside the scope of the Code. The General Medical Council advised doctors to act in patient's best interest when, *inter alia*, arranging treatment.

Promoting the use of a brand instead of a generic was not necessarily a breach of the Code. It was unacceptable for companies to pay for or facilitate switches. The complainant alleged that his manager had trained him to offer a switch service or payment for one to be carried out and that this was evidenced in a field visit report. The letter to the NHS chief executives stated that the manager advised a surgery that had refused to use branded Flomaxtra, to prescribe tamsulosin tablets as only Flomaxtra could fill such a prescription. The complainant alleged that there was no clinical need to move patients from generic tamsulosin capsules and that the heavy handed promotion of Flomaxtra was completely misleading.

The Panel noted each party's comments. The field visit report showed that patients at one surgery on tamsulosin capsules were switched to Flomaxtra but not that Astellas had paid for or otherwise facilitated the switch. The prescribers decided which patients to switch. There was no evidence that the discount offered to dispensing doctors was offered as a payment to switch patients. The Panel ruled no breach of the Code.

In relation to the meeting, the Panel noted the letter about the meeting, signed by three consultants on NHS trust headed paper, provided by the complainant was different to the copy provided by Astellas in that the Astellas copy stated at the bottom of the page 'This meeting is wholly sponsored by Astellas Pharma Ltd'. Both versions stated that Astellas had agreed to sponsor the meeting. The original invitation included the company logo and a number of references to Astellas' role.

The Panel noted that the letter from the consultants started with details about the venue, programme and speakers. It went on to explain that Astellas had agreed to sponsor the meeting and the consultants had asked the company to invite GPs who referred patients to their urology service. The letter stated that it would be helpful if one GP from each practice attended. There was no mention of mandatory attendance. It could be argued that the impression was given that the meeting was an NHS-led meeting with sponsorship from Astellas and not an Astellas-led promotional meeting. Astellas denied the allegations that the manager had directed the complainant to refer to the meeting as an NHS meeting and that attendance was mandatory. The Panel noted that the letter from the consultants did not refer to the meeting as an NHS meeting. The letter was on NHS headed paper and would appear to recipients to endorse the meeting. It was the second mailing about the meeting. The proforma to reserve a place was to be returned to Astellas and referred to the invitation already received from Astellas. On balance the Panel considered that overall the nature of the meeting should have been made clearer in the letter but the letter did not disguise the nature of the meeting as alleged. The Panel ruled no breach of the Code in this regard. The Panel noted that branded items had been available to the meeting attendees. There was no complaint about the actual items. The Panel noted that providing branded promotional items at the promotional meeting was not unacceptable. No breach was ruled. The Panel did not consider that the letter from the consultants or the use of the branded items meant that high standards had not been maintained. No breach was ruled including Clause 2.

The Panel was concerned by the complainant's statement that attendees had complained that the meeting was a disguised promotional activity and that the use of NHS logos was misleading and offensive. The Panel noted its comments about the letter from NHS consultants. It considered that the relationship between the NHS, the consultants and Astellas in relation to the meeting should have been made clearer but that in the circumstances the use of the NHS logo was not misleading or offensive. No breach was ruled in this regard.

The delivery of attendance certificates after the meeting was not necessarily a breach of the Code. There was no evidence that the representatives had used either the invitation or the attendance certificates as inducements to gain an interview. No breach was ruled.

The complainant alleged that his manager forced him to encourage GPs to prescribe Zineryt 90ml excessively. The Panel noted that there was no evidence in this regard. The briefing material for the detail aid stated that the 90ml pack size was for patients with acne more widespread than just on the face. The Panel ruled no breach of the Code.

A former employee of Astellas Pharma Ltd complained about the company's promotional practices.

COMPLAINT

The complainant stated that the number of breaches of the Code by Astellas, and their severity, brought the industry into disrepute and abused the limited public funds provided to the NHS. The complainant provided a copy of a letter which he had sent to two local NHS chief executives detailing the breaches.

Clause 2 – Discredit to, and reduction of confidence in the industry

The complainant stated that majority of the points discussed in the letter to two NHS chief executives fell under this clause.

a) Inducement to prescribe – offering doctors excessive payments to switch their patients from cheaper generic products on to more expensive Astellas branded products.
b) Prejudicing patient safety – encouraging doctors to undertake 'blanket' switches with excessive payments for their time, thus neglecting patient welfare.
c) Misleading promotional activities – the meetings described as NHS meetings were promotional meetings which were knowingly mis-described to GPs.
d) Misleading sales activities – due to extremely low sales of Zineryt (available in both 30ml and 90ml) the complainant's manager forced him to encourage GPs to prescribe 90ml excessively when not needed, to bring in higher sales. This caused great wastages due to the limited shelf life of the product, and was a complete waste of patient welfare and public funds.

Clause 9 – High standards, format, suitability

The various promotional meetings had invitations with letters attached with an NHS logo requesting the attendance of the GP. The meeting was sold as an NHS meeting, yet was a promotional activity for the company. The delegates all complained afterwards that the meeting was a disguised promotional activity and that the use of NHS logos was very misleading and caused offence.

Clause 12 – Disguised promotion

The meetings discussed in Clause 9, though billed as an NHS meeting were promotional activities. The

complainant stated that his manager asked him to telephone surgeries, or call in person, to confirm they had received their 'NHS urology meeting invitation', and inform them that attendance was mandatory as they had been written to by the urology department. All delegates at the meeting received large branded 'goody' bags with branded items to further enhance brand awareness.

Clause 14 – Certification

The delegates who attended the NHS meeting were given attendance certificates which Astellas used as 'access tools' to follow up all the promotional messages delivered at the meeting.

Clause 15 – Representatives

Representatives must not employ any subterfuge to gain an interview: during the promotion of the NHS meeting the complainant was directed to call on GPs and state that he was 'delivering a letter of importance from the NHS, it is important I see the Dr …'. Furthermore after the meeting the attendance certificates were used as access tools to secure an interview. Both activities were in breach of Clause 15.

Clause 18 – Inducements

During a promotional call with a dispensing GP, the commercial discounts were also calculated for the surgery. This was a breach of the Code. Once the profits had been calculated for the surgery, GPs were then advised that Astellas could either offer an intervention service to switch all patients from generic products onto branded products, or offer the GP excessive payment to cover the time they would need to do the switch themselves. This was a direct inducement to prescribe the company's products, in breach of Clause 18. This activity was evidenced in the field visit report carried out by the complainant's manager, who trained him to carry out the call like this. Following on from the call the complainant received a congratulations card (provided) and chocolates as a gift for securing a switch program.

The complainant considered that it was his moral and professional duty to bring such violations to the Authority's attention as it was clear that the conduct of Astellas brought the rest of the industry into disrepute.

When writing to Astellas, the Authority asked it to respond in relation to Clauses 2, 9.1, 12.1, 14, 15.3, 18.1 and 18.4 of the Code.

RESPONSE

Astellas noted that the complainant had provided no evidence to show that the company had paid doctors to switch patients to its medicines as alleged. Astellas submitted that no health professional had been paid to switch patients, review patients on other treatments or encourage them to use Astellas products. Astellas' representatives had encouraged GPs to carry out a simple switch from other products within the same therapeutic class to Astellas medicines because of the benefits of the particular brand. This was not a breach of the Code in itself and no payments, inducements or benefits in kind had been given either directly or through a third party in order to make this happen.

The complainant had alleged that 'blanket switch' programmes had prejudiced patient safety but had provided no supporting evidence. Astellas submitted that no 'blanket switch' programmes had been undertaken and that no payments had been made to health professionals. Representatives were paid to promote their product consistently with the Code and Astellas had no evidence that anything to the contrary had occurred.

It was alleged that Astellas ran promotional meetings disguised as NHS meetings. Astellas stated that it supported a number of different types of meetings including company-led meetings and NHS-led meetings. All such meetings were conducted in line with the Astellas external meetings policy which required that an accurate acknowledgement of the extent of Astellas' involvement with the meeting was declared. Copies of briefing documents for all Astellas meetings were available along with approved invitations that had been sent out. Astellas could find no evidence of disguised promotion.

The meeting that was referred to in point 2 of the complaint was an Astellas-led promotional meeting. The invitation, meeting approval form and speaker briefs were provided. Such briefings and invitations were template documents which had been certified and the representative could add speaker names and presentation topics. These briefs and invitations were then checked for Code compliance by the representative's business manager and, if the meeting had a budget of £500 or more, by the Astellas medical department. For this meeting the invitations and briefs were examined by both the business manager and the medical department. The invitation made it clear that this was an Astellas meeting; Astellas was mentioned seven times, not including the Astellas logo. Specifically there were three separate declarations that this meeting was 'wholly sponsored by Astellas Pharma Ltd'. Astellas failed to understand how any recipient could not be clear that this meeting was an Astellas meeting and not an NHS-led meeting. The meeting was initially scheduled to run for 2 hours with all three local urologists speaking on the management of overactive bladder in primary care, urinalysis and the local referral pathway for suspected urological cancers. The urologists were particularly keen to explain the local referral process and pathway for suspected urological cancers to the local GPs and they asked if Astellas would send a second mailing consisting of a letter signed by all three urologists as they did not have the resources to do this. As this was an unusual request, this was seen by the Astellas medical department and because it was made clear in both the text and the declaration on

the bottom of the letter that this was an Astellas meeting, the company agreed to send the letter on behalf of the consultants since the 2 week maximum wait was an NHS target and this was an important disease area. Astellas noted that the copy of the consultants' letter which the Authority received did not include the declaration 'This meeting is wholly sponsored by Astellas Pharma Ltd' on the bottom and the company could only speculate as to how this happened. However Astellas had a digital copy of the original and the declaration that the meeting was wholly sponsored by Astellas was stated at the foot. Astellas was clear that this was not an attempt to suggest this was an NHS-led meeting. A reply slip was enclosed with the consultants' letter which was written by the local representative. However this contained only a form to capture administrative details and referred to the previous invitation sent by Astellas.

Astellas noted that it chose the three speakers but due to unforeseen circumstances, one had to withdraw from the meeting at very short notice. Astellas' medical sales representative briefed the remaining two speakers according to Astellas' electronic field notes. Copies of both presentations were provided. One speaker used a certified slide kit from Astellas as the basis for his talk which he subsequently modified. However the modifications were consistent with the Code. The other speaker projected the hospital referral pathway document on screen and did not use slides.

The complainant stated that 'the delegates all complained' after the meeting because they were not aware of it being an Astellas meeting. The manager was not at the meeting but neither he nor the other medical representative who was present received any complaints about disguised promotion. Surprisingly for such a serious accusation, the complainant raised no concerns beforehand and did not mention any customer complaints to his manager after the meeting. The first Astellas had heard of any issue was in the complainant's letter to the Authority just over one year later. There appeared to be no evidence to support this allegation and the supporting materials strongly supported Astellas' view that the complainant's statements were not true.

The complainant stated that his manager told him to say this was an NHS meeting and that attendance was mandatory when calling upon doctors to remind them about the meeting. The manager categorically denied this and it was clear from both the supporting documentation and simple common sense that these would not have been credible statements to make. The manager understood that it was in breach of the Code to proactively telephone customers for any reason and so he had never instructed any of his representatives to do so. The manager denied that he had directed the complainant to 'telephone surgeries or call in person, to confirm they had received their NHS urology meeting invitation, and inform them that attendance was mandatory as they had been written to by the urology department'. Astellas provided a copy of the email sent to the complainant and his territory counterpart to drive attendance to the meeting; the manager simply stated 'Let's do all we can to make this a fantastic meeting which means pulling out all the stops to drive attendance'. By this he meant ensuring that all of the relevant surgeries had a copy of the Astellas approved invitation. The manager recalled that around this time, the complainant was absent from work and was not heavily involved in promoting this meeting to GPs until one to two days before it took place.

It was also stated that 'goody bags' were given out to delegates with branded items to 'enhance brand awareness'. Astellas submitted that plastic delegate bags most likely containing branded post-it pads, pens, patient bladder diaries, overactive bladder algorithm leaflets and the like would have been available. Astellas did not know exactly what promotional items had been available on the night since the meeting took place over a year ago but to give out such items which were all certified and had an actual and perceived value of less than £6 (excluding VAT) was not a breach of the 2008 Code and this was one point on which Astellas agreed with the complainant.

Astellas strongly considered that this meeting was not in breach of Clauses 9.1, 12.1, 14 or 2.

Astellas denied the complainant's allegation that attendance certificates were used as 'access items' after such meetings. No certificates were available at Astellas' speaker meetings because typically over 100 invitations were sent (over 400 for this event) and the actual attendance was just 20. Names were taken and a printed certificate was delivered afterwards but all representatives were briefed that they could not use it to gain an interview and it must be left with the receptionist if requested. Astellas confirmed separately with another member of the manager's team that the team had all been verbally briefed on several occasions that certificates and requested items via reply-paid cards must be left with receptionists if required and specifically that they must not be used to gain an interview. This was in addition to the training provided when representatives joined Astellas. The complainant's version of events seemed to be at variance with those of the manager and his team.

The complainant stated he was instructed to use subterfuge to gain an interview by stating he was 'delivering a letter of importance from the NHS'. No such direction was given by the manager around gaining an interview using invitations to an 'NHS meeting'. Representatives might have asked to see a GP to discuss a forthcoming meeting of interest but this was a normal promotional activity relating to any territory meeting that was imminent. There was never an instruction to disguise this as an NHS meeting. In summary there was no evidence of any breach of Clause 15.3.

Astellas noted the allegation that, with regard to Zineryt, the complainant's manager had forced him

during field visits to encourage GPs to prescribe 90ml excessively when not needed. This was alleged to have been due to low sales in the region. Zineryt at the time was the most widely prescribed topical acne brand in the UK and the sales data for the regions mentioned were no different from the rest of the country. No encouragement had been made within the region to ask health professionals to use Zineryt 90ml when the 30ml presentation would be more appropriate. Zineryt, once reconstituted, had a 5-week shelf life after which any unused solution should be discarded. Zineryt 90ml should therefore be prescribed where the patient had acne over an extended area such as the face, neck, bib area, shoulders and accessible parts of the back. This strategy was in line with the national operational plan and briefing document at the time. The sales aid in use at that time which also doubled as a leavepiece, made it clear that Zineryt 90ml was intended for larger areas of acne. The manager could not recall an instance when the complainant inappropriately sold Zineryt 90ml so there was no evidence on this specific issue. Astellas believed high standards had been maintained and thus it denied a breach of Clause 9.1.

The complainant stated that he breached the Code by discussing commercial discounts during a promotional call. Astellas was puzzled by this and thought this had arisen from a communication from the manager. The manager had issued guidance to his representatives regarding the need to keep 'clinical' (ie promotional) calls separate from commercial calls. Astellas was not aware that this was in itself a breach of the Code; it was simply the manager's preferred way of working. However in feedback to the complainant, the manager had insisted that the complainant keep discount discussions with dispensing GPs separate from a promotional call. The complainant was informed of the manager's instruction in this regard in an email dated 4 December 2009 which was provided. Astellas failed to see how mixing promotional discussions with discount discussion with dispensing GPs was a breach of the Code. Discounts were exempt under Clause 18.1 (supplementary information) as they were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. The Code did not state that such discussions could not take place in the same call and indeed this would be common practice in the industry in Astellas' experience.

Astellas noted the allegation that it could 'offer an intervention service to switch all patients from generic products onto branded products, or offer the GP excessive payment to cover the time they would need to do the switch themselves'. It was alleged that these practices were evidenced in the manager's field report accompanying the complaint. Astellas could find no mention of such activities in the field visit report. The only mention of products being transferred or switched were the doctor's agreed actions as a direct result of the sales call – 'transfer of [tamsulosin capsules] to Flomaxtra' which was exactly what was expected of the representative. There was no financial inducement or 'switch service', both of which would have been serious breaches of Clause 18. The sales call that the complainant referred to with the coaching report was, from the manager's recollection, solely a promotional call following a commercial call with the dispenser at which the manager was not present. The GP in question raised the cost of the branded generic form of tamsulosin capsules that the practice used and the fact that the practice lost money by using it (the tariff price was apparently lower than cost of the medicine). As a result, the GP volunteered to review patients on tamsulosin capsules and move suitable patients to Flomaxtra if they fitted the criteria he devised. This was highlighted on the feedback form (dated 2 June 2009) in terms of the outcomes from the call. Further discussion around this outcome from the complainant to the marketing department was contained in an email (provided) which clearly showed that no financial inducement or third party 'intervention' service was used to effect these switches.

Once again these allegations seemed to be without foundation and no supporting evidence was offered to substantiate them. Indeed the evidence to refute them included an email from the complainant in which he detailed exactly what he did to achieve the switches and offered a completely rational explanation for the decision made by the practice, all in a manner compatible with the Code (Clause 18.4, supplementary information).

Astellas offered a therapy review service in the separate area of overactive bladder which was a fully certified programme run by a third party but none of the complainant's customers had ever used it.

In summary a great many of the complainant's allegations had been made without any evidence to substantiate them. Astellas took its responsibilities to adhere to the Code seriously and strongly refuted any breaches of Clauses 2, 9.1, 12.1, 14, 15.3, 18.1 and 18.4.

PANEL RULING

The Panel noted that the complainant, an ex-employee of Astellas, had made a number of serious allegations including some about the conduct of his manager. Astellas denied all the allegations. It appeared that much of this case related to one person's word against another. It was difficult in such cases to determine where the truth lay. As stated in the introduction to the Constitution and Procedure a complainant had the burden of proving their complaint on the balance of probabilities. In this case the complainant had provided very little material to support his position. A judgement had to be made on the available evidence.

The Panel noted that more detail about the allegations was included in the letter the complainant sent to the NHS chief executives, a

copy of which he provided to the PMCPA. The Panel considered the case as follows.

Alleged inducements to prescribe

The complainant had called upon dispensing doctors and considered that the Code required discussions about discounts to be separated from the promotion of those medicines' clinical benefits. This was not necessarily so. All claims about a product, including cost and discussions about discounts had to comply with the Code. Such activities were promotional and the Panel considered that, provided that the requirements of the Code were otherwise met particularly Clause 18.1, clinical and commercial discussions could occur in the same call. It appeared that the complainant's manager preferred his representatives to discuss the two topics in separate calls which might be prudent but it was not a breach the Code *per se* to do otherwise. No detailed allegations had been made. The Panel ruled no breach of Clause 18.1.

The supplementary information to Clause 18.1, Terms of Trade, stated that measures or trade practices relating *inter alia* to discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 were outside the scope of the Code and excluded from Clause 18.1. The General Medical Council advised doctors to act in a patient's best interest when, *inter alia*, arranging treatment. This was also included as supplementary information to Clause 18.1.

Promoting the use of a branded product instead of a generic medicine was not necessarily a breach of the Code. The supplementary information to Clause 18.4, Switch and Therapy Review Programmes, made it clear that it was unacceptable for companies to pay for or facilitate switches. The complainant alleged that his manager had trained him to offer a switch service or payment for one to be carried out and that this was evidenced in a field visit report. The letter to the NHS chief executives stated that the manager advised a surgery that had refused to use branded Flomaxtra, to prescribe tamsulosin tablets as only Flomaxtra could fill such a prescription. Tamsulosin capsules were available generically. The complainant alleged that there was no clinical need to move patients from generic tamsulosin and that the heavy handed promotion of Flomaxtra was completely misleading.

The Panel noted each party's comments. The field visit report showed that patients at one surgery on tamsulosin capsules were switched to Flomaxtra but not that Astellas had paid for or otherwise facilitated the switch. The prescribers decided which patients to switch. There was no evidence that the discount offered to dispensing doctors was offered as a payment to switch patients as prohibited by Clause 18.4. The Panel ruled no breach of Clauses 18.1 and 18.4 and thus no breach of Clause 2.

Meeting – 25 November 2009

The Panel noted the letter signed by three consultants on NHS trust headed paper provided by the complainant was different to the copy provided by Astellas in that the Astellas copy stated at the bottom of the page 'This meeting is wholly sponsored by Astellas Pharma Ltd'. Both versions of the letter stated that Astellas had agreed to sponsor the meeting. The original invitation included the company logo and a number of references to Astellas' role.

The Panel noted that the letter from the consultants started with details about the venue, programme and speakers. It went on to explain that Astellas had agreed to sponsor the meeting and the consultants had asked the company to invite GPs who referred patients to their urology service. The letter stated that it would be helpful if one GP from each practice attended. There was no mention of mandatory attendance. It could be argued that the impression was given that the meeting was an NHS-led meeting with sponsorship from Astellas and not an Astellas-led promotional meeting. Astellas denied the allegations that the manager had directed the complainant to refer to the meeting as an NHS meeting and that attendance was mandatory. The Panel noted that the letter from the consultants did not refer to the meeting as an NHS meeting. The letter was on NHS headed paper and would appear to recipients to endorse the meeting. It was the second mailing about the meeting. The proforma to reserve a place at the meeting was to be returned to Astellas and referred to the invitation already received from Astellas. On balance the Panel considered that overall the nature of the meeting should have been made clearer in the letter but the letter did not disguise the nature of the meeting as alleged. The Panel ruled no breach of Clause 12.1 in this regard. The Panel noted that branded items had been available to the meeting attendees. There was no complaint about the actual items which would be promotional. The Panel noted that providing branded promotional items at the promotional meeting was not unacceptable. No breach of Clause 12.1 was ruled. The Panel did not consider that the letter from the consultants or the use of branded items at a promotional meeting meant that high standards had not been maintained. No breach of Clause 9.1 was ruled. The Panel did not consider the circumstances warranted a breach of Clause 2 and ruled accordingly.

The Panel was concerned by the complainant's statement that attendees had complained that the meeting was a disguised promotional activity and that the use of NHS logos was misleading and offensive. The Panel noted its comments about the letter from NHS consultants. It considered that the relationship between the NHS, the consultants and Astellas in relation to the meeting should have been made clearer but in the circumstances the Panel did not consider that the use of the NHS logo was misleading or offensive. No breach of Clause 9.1 was ruled in this regard.

The delivery of attendance certificates after the meeting was not necessarily a breach of the Code. There was no evidence that the representatives had used either the invitation or the attendance certificates as inducements to gain an interview. No breach of Clause 15.3 was ruled. The provision of attendance certificates was not covered by Clause 14 which dealt with company approval of its materials and activities. No breach of Clause 14 was ruled.

Promotion of Zineryt 90ml

The complainant alleged that his manager forced him to encourage GPs to prescribe Zineryt 90ml excessively. The Panel noted that there was no evidence in this regard. The briefing material for the detail aid stated that the 90ml pack size was for patients with acne more widespread than just on the face. The Panel ruled no breach of Clause 2.

Complaint received **22 November 2010**

Case completed **11 March 2011**

CASE AUTH/2372/11/10

FORMER EMPLOYEE v ALCON LABORATORIES

Promotion of Travatan

A former employee complained that Alcon Laboratories had promoted a formulation of Travatan (travoprost) that was not preserved with benzalkonium chloride (BAK) before the marketing authorization for that formulation had been granted. [The reformulated eye drops were preserved with Polyquad]. Travatan was indicated for the management of ocular hypertension or open-angle glaucoma.

The complainant had emails which showed her manager had asked her to visit all customers after a speaker meeting to 'discuss the potential of BAK-free'. She believed that a competitor company had contacted Alcon and that Alcon had denied all allegations. Five days later, her manager and the other two regional managers telephoned some representatives, not all, to ask them not to discuss BAK-free Travatan. The complainant's call notes and those of a number of other representatives showed that they had discussed this on every available opportunity. The complainant alleged a breach of Clause 2.

An email provided by the complainant referred to an enquiry from a formulary pharmacist to a representative about Polyquad and the response from Alcon referred to slides on Polyquad and listed its properties. The complainant stated that the email, from the Travatan brand manager, was to help representatives to understand what Polyquad was and how the representatives could sell it to their customers.

Another email, from her manager referred to the need to build on the endorsement of Azarga by the speaker at a meeting, his attempt to limit Lumigan use, and the potential of BAK-free. A 1:1 follow-up was stated to be crucial within ten days of the event.

The detailed response from Alcon Laboratories is given below.

The Panel noted that when it received the complaint Travatan preserved with Polyquad was still the subject of a product licence variation. The formulation for which Alcon held a licence at that time was Travatan preserved with BAK. At a meeting held on 30 September/1 October, representatives were briefed on the revised formulation. They were instructed that if ophthalmologists asked them about BAK-free Travatan they were to 'Explain that Alcon will introduce (within the new year) NEW Travatan BAK FREE soon, and explain that the new formulation has proven to be as powerful as the existing Travatan but with a better tolerability profile'. The Panel noted that this instruction went beyond Alcon's submission to the Authority that representatives could simply inform customers of the regulatory status of BAK-free Travatan if asked.

The Panel noted that as a result of this complaint, Alcon emailed its representatives on 24 November and asked them to ensure that there were absolutely no conversations about Travatan BAK-free until it had a product licence. An analysis of the call records showed that one representative in particular regularly referred to BAK-free Travatan from early October until early November. A typical entry by that individual read 'Briefly mentioned Travatan in terms of absolute IOP [intra-ocular pressure] drop, control of diurnal fluctuations, tolerability, price and future BAK free formulation'. It appeared from the call notes that any discussion about BAK-free Travatan had been initiated by the representative and not a health professional. In that regard the Panel noted Alcon's submission that the content of call notes was often not scrutinised in detail and that any indication that a representative had not adhered to company policy might not be picked up at the time unless the practice was widespread. The Panel was concerned about the company's approach which it considered was unacceptable.

The Panel noted that Alcon's product, Systane (a device), was an ocular lubricant preserved with Polyquad and could be promoted. Representatives were instructed to reinforce the message that Systane did not contain BAK, that BAK was associated with ocular surface toxicity and that Polyquad did not exhibit the same ocular surface toxicity as BAK. Representatives were also encouraged to use the promotion of Systane to raise the subject of dry eye in glaucoma patients and its potential link to the presence of BAK in eye drops used for treatment and to assess the level of interest in this topic to assist targeting of future sales activity. In the Panel's view it was likely that the discussion of Systane and problems of dry eye in glaucoma would solicit questions about BAK-free treatments for the condition.

The Panel considered that, on the balance of probabilities, Alcon representatives had promoted BAK-free Travatan before the grant of a marketing authorization which permitted the sale or supply of that formulation. A breach of the Code was ruled.

The Panel further considered that the presentation used to brief the representatives in September/October, which encouraged them to discuss and make claims for Travatan BAK-free, advocated a course of action which was likely to lead to a breach of the Code. A breach of the Code was ruled.

The Panel considered that high standards had not

been maintained. A breach was ruled. The Panel, however, did not consider that the activity was such as to bring discredit upon the industry and no breach of Clause 2 was ruled.

A former employee complained that Alcon Laboratories U.K. Limited had promoted a formulation of Travatan (travoprost) that was not preserved with benzalkonium chloride (BAK) before a marketing authorization for that formulation had been granted. [The reformulated eye drops were preserved with Polyquad]. Travatan was indicated for the management of ocular hypertension or open-angle glaucoma.

COMPLAINT

The complainant alleged that Alcon had actively promoted BAK-free Travatan. She believed this was yet to gain a licence in the UK. She had emails which showed her manager had asked her to visit all customers after a speaker meeting to 'discuss the potential of BAK-free'. She believed that a competitor company had contacted Alcon and that Alcon had denied all allegations. Five days later, her manager and the other two regional managers telephoned some representatives, not all, to ask them not to discuss BAK-free Travatan. The complainant's call notes and those of a number of other representatives showed that they had discussed this on every available opportunity. The complainant alleged a breach of Clause 2 of the Code.

An email provided by the complainant referred to an enquiry from a formulary pharmacist to a representative about Polyquad and the response from Alcon referred to slides on Polyquad and listed its properties. The complainant stated that the email, from the marketing department, was to help representatives to understand what Polyquad was and how the representatives could sell it to their customers.

Another email from her manager referred to the need to build on the endorsement of Azarga by the speaker at a meeting, his attempt to limit Lumigan use, and the potential of BAK-free. A 1:1 follow-up was stated to be crucial within ten days of the event.

The complainant stated that after she had left Alcon, former colleagues had told her that the representatives had been asked by email to no longer promote BAK-free as there had been a complaint from the ABPI.

When writing to Alcon, the Authority asked it to respond in relation to Clauses 3.1, 9.1 and 15.9 in addition to Clause 2 cited by the complainant.

RESPONSE

Alcon noted that, from the documents presented, the complaint appeared to relate to promotional activity that took place between the beginning of October and 24 November 2010, the date that the Authority received the complaint.

The medicine at issue was 'Travatan BAK-free'. No such medicine existed or would exist in the future. Alcon had held a marketing authorization for Travatan since November 2010 and had recently reformulated it to replace the existing preservative, benzalkonium chloride (BAK), with polyquarternium-1 (Polyquad). Alcon obtained approval from the EMEA to market the reformulated product on 29 November 2010 and would commence marketing activities early in 2011. This was not the introduction of a new product but simply the reformulation of an existing one. The new formulation would replace the original formulation and apart from a short transition period, the two formulations would not co-exist.

Alcon had known that approval for the revised formulation was imminent for a number of months and had prepared internally for the change. To this end, the sales force was briefed at a meeting held between 30 September and 1 October 2010 to outline Alcon's sales and marketing strategy. The representatives had to be briefed then because Alcon expected to obtain the approval for the new formulation before the next scheduled meeting in January 2011 and with the intervening Christmas holiday period, it was clear that time for any interim launch meeting would be limited. A copy of the slides used in this briefing was provided. The representatives were not given a copy of the slides, nor were they given any other training or promotional material about the new formulation. It was the misrepresentation of the strategy outlined at this sales meeting, either deliberately or unintentionally, that formed the basis of this complaint.

Alcon explained that it had been known for some time that BAK was toxic to mammalian cells and that the repeated use of eye drops containing it could produce signs and symptoms of ocular surface disease such as dry eye and conjunctival inflammation. BAK was the preservative used in most eye drops marketed in the UK. Most eye drops were for short-term use only and so significant problems relating to the preservative were not encountered. However, in chronic, incurable ophthalmic conditions, such as dry eye and glaucoma, it was now recognised that the repeated exposure to BAK represented a significant clinical issue in certain patients. In some dry eye patients their condition might be worsened by treatment, a condition recognised by the diagnostic term 'ophthalmia medicamentosa'. It had also been documented that glaucoma patients might develop dry eye and/or other ocular surface disease once they started to use eye drops and that their signs and symptoms could be directly related to the number of different BAK-containing eye drops that they used. These issues had been the subject of numerous publications and had been extensively reviewed at international ophthalmic congresses and meetings.

In recent years there had thus been increased interest in the development of ophthalmic products for use by dry eye and/or glaucoma patients that did not contain BAK. This was evidenced by the introduction of many

new unpreserved, single use ocular lubricant products onto the UK market. Multidose ocular lubricants containing alternative, less toxic preservatives had also been introduced, such as Alcon's own product Systane which was preserved with Polyquad. Polyquad had been used for many years in contact lens care products and had been repeatedly shown, *in vitro* and *in vivo*, to be less toxic to ocular tissue than BAK.

With regard to anti-glaucoma products, unpreserved, single use presentations had become available and interest in the issues surrounding BAK within the ophthalmic community had reached unprecedented levels. Alcon noted that the specialist ophthalmic community in the UK was relatively small and very well informed. It would therefore be very difficult to find a UK ophthalmologist who was not aware of recent research relating to the effects of BAK and the efforts to formulate products without it.

The UK ophthalmic community knew that Alcon planned to introduce a variant Travatan formulation that did not contain BAK, for two main reasons:

1 Alcon had marketed a Travatan BAK-free variant in the US since October 2006 (Travatan Z). Travatan Z did not contain Polyquad but was preserved with an alternative proprietary preservative system called sofZia and had been the subject of numerous published papers. In addition, it had been promoted in many of the international ophthalmology journals which although published in the US, and had the majority of their circulation there, represented an important information resource for UK ophthalmologists.

2 Scientific posters and presentations detailing research studies conducted on a formulation of travoprost (the active ingredient in Travatan) preserved with Polyquad were presented at the 9th European Glaucoma Society Congress held in Madrid in 2010.

As the first multidose prostaglandin analogue to be available without BAK, interest in Travatan Z amongst UK glaucoma specialists had been particularly marked. Alcon noted that the cost of currently available unpreserved, single-dose anti-glaucoma eye drops was approximately 39% to 200% more than similar multidose therapy and therefore the introduction of more reasonably priced alternatives was eagerly awaited, as it had significant budgetary implications.

Alcon's representatives called almost exclusively on ophthalmologists who were specialists in glaucoma, all of whom were well acquainted with the facts outlined above. As a result, Alcon's representatives had frequently been asked about availability of a BAK-free formulation of travoprost even though they had always been instructed not to initiate such a discussion.

Alcon addressed each allegation separately.

'Alcon had actively promoted BAK-free Travatan' (presumably meaning the new Travatan formulation, preserved with Polyquad), which 'was yet to gain a license in the UK'.

Alcon submitted that this allegation was untrue and unfounded. As stated above it had informed the sales force about the intended reformulation of Travatan and had provided it with a detailed briefing about the sales and marketing strategy to be adopted once approval of the formulation was obtained. However, representatives had not been instructed to detail the new formulation and had been given no support material to enable them to do so.

At the sales meeting referred to above, Alcon's representatives were instructed that four products would remain on detail for each call for the final quarter of 2010 ie Travatan, Systane, Azarga and Duotrav. Three of these, Travatan, Azarga and Duotrav, were anti-glaucoma products and Systane, as noted above, was an ocular lubricant preserved with Polyquad. For Travatan, the instructions for the cycle were to reinforce Alcon's competitive position with regards to efficacy and safety, in preparation for the increased marketing activity that would take place once the reformulated product was introduced. This did not include active promotion of the reformulated product, although representatives were told that they could now respond to any customer enquiries by stating that the product was expected to be available in the New Year. Alcon did not consider that this instruction was in breach of the Code since the Code did not apply to 'replies made in response to individual enquiries from members of the health professions or appropriate administrative staff'.

As part of their promotional activities for Systane representatives were also instructed to reinforce that: Systane did not contain BAK but was preserved with Polyquad; BAK was associated with ocular surface toxicity and Polyquad did not exhibit the same ocular surface toxicity as BAK.

Representatives were also encouraged to use the promotion of Systane to raise the subject of dry eye in glaucoma patients and its potential link to the presence of BAK in eye drops used for treatment and to assess the level of interest in this topic, to assist in future targeting of sales activity. To help in this activity, information about BAK and Polyquad was reviewed at the sales meeting and copies of the slides presented were provided. Once again, the representatives were not given copies of these slides.

Promotion of Systane in association with anti-glaucoma products was justified because most glaucoma patients were elderly and the incidence of dry eye disease increased with age and the incidence of dry eye in glaucoma patients was known to be higher than in the population as a whole. It had also been demonstrated that the severity of signs and symptoms of ocular surface disease (including dry eye) in glaucoma patients was directly related to the number of products containing BAK that were used and therefore use of an ocular lubricant preserved

with BAK could make the situation worse.

Systane was not a licensed medicine, although it was listed in the Drug Tariff as a prescribable medical device, and so promotion of this product did not come under the scope of the Code. However, even if it did, the method of promotion described above did not contravene the Code. Clearly, dissemination of information about the potential toxicity of BAK and the comparative performance of Polyquad would be beneficial to Alcon when the Polyquad formulation of Travatan was launched. However, the activities outlined above did not constitute promotion of an unlicensed product. They also did not represent 'teaser advertising' since the activity was not directly linked to promotion of Travatan and substantial information was provided about the preservative contained in Systane in which the intended audience had a legitimate interest and reason to prescribe. Alcon noted that promotion of medicines under the Code did not cover the provision of 'information relating to human health or diseases provided there is no reference, either direct or indirect, to specific medicines' and therefore, in Alcon's opinion, did not cover general discussions about the effects of preservatives in glaucoma patients.

Alcon noted that six items of 'evidence', which claimed to support the allegation, were referenced in the correspondence. Alcon's additional comments on each item were detailed below.

1 **Email from a regional business manager,** 'asking the complainant to 'visit all customers after a speaker meeting to ''discuss the potential of BAK-free.'''

The speaker meeting referred to in this email was an authorized promotional event at which a contracted consultant spoke in support of Azarga, which was also used to treat glaucoma; Travatan was not the subject of the meeting. However, as stated above, the potential problems relating to the use of BAK in glaucoma patients and the availability of a BAK-free formulation of Travatan was common knowledge within the ophthalmic community and during the discussion session at the end of the meeting a member of the audience asked about availability of such a product in the UK. This question was answered in the negative by the speaker, although he did mention that such a product would be available in the near future.

The email was sent to the two representatives who had organised the meeting and encouraged them to build on the speaker's endorsement of Azarga and comments that he made about a competitor product, Lumigan, and also to discuss the potential of 'BAK-free'. This last comment was not to encourage the representatives to promote Travatan outside of the terms of its marketing authorization but to follow the cycle strategy outlined above. All of these instructions were in line with the promotional strategy for this cycle, outlined above.

2 **Hearsay (unsubstantiated),** 'I (the complainant) believed that a [competitor company] had contacted […],Alcon and he had denied all allegations. Five days later, […] and the other two regional managers had telephoned some representatives, not all, to ask them not to discuss BAK-free Travatan.'

Alcon submitted that on 10 November 2010, it received a telephone call from the medical director of a competitor company suggesting that Alcon had promoted a Polyquad preserved formulation of Travatan. This accusation clearly misinterpreted the nature of Alcon's promotional activity and was therefore denied. However, as a result of this call and a follow-up email Alcon's regional business managers were instructed to reinforce the nature of the intended promotional activity to their representatives and to ensure that the Polyquad preserved formulation of Travatan was not directly mentioned in association with this activity. A copy of relevant email correspondence was provided. This correspondence was entirely compatible with the promotional activity already outlined. The competitor company had not taken the matter any further and Alcon submitted that if it had 'actively promoted' the reformulated product, as alleged, the competitor company would surely have been able to gather evidence to pursue a complaint.

3 **Hearsay (unsubstantiated),** 'Myself [the complainant] and a number of representatives have call rates in Alcon's call reporting system which stated that they had discussed this on every available opportunity.'

As stated previously, it was Alcon's intention that its representatives should discuss the potential problems with BAK and the benefits of Polyquad as part of their promotion of Systane and that they could confirm the impending availability of a BAK-free formulation of Travatan if directly questioned. It was not surprising therefore that this should have been mentioned in a representative's call notes. Unfortunately, these call notes were generally used to monitor call patterns and activity and the content was often not scrutinised in detail. Any indication that certain representatives had not adhered to stated company policy with regard to the promotion of Travatan might therefore not necessarily have been noted at the time, unless it was widespread.

As a result of this complaint, Alcon had reviewed its call reporting system records for the complainant's manager's representatives for the period from the last sales meeting to the end of November and found no notes of the type mentioned. However, 40 reports from 3,552 mentioned 'Travatan BAK-free' or 'BAK-free' in association with Travatan rather than Systane. Alcon noted that it had generally been impossible to tell from the report whether any discussion recorded was initiated by the representative or the doctor. Alcon summarised each representative's reports and noted that 22 of the 40 reports (55%) related to one person. Five representatives reported mentioning the reformulated Travatan. Five representatives had not mentioned the reformulated product. Full details of

the reports were provided.

In Alcon's view, the pattern of reporting was not consistent with the allegation of 'active promotion' of the reformulated product but was consistent with the promotional strategy outlined above.

4 **Email from Alcon sent to sales** representatives containing information 'to help them understand what Polyquad was and how they could sell to their customers'.

Alcon submitted that since Systane was actively promoted, it was understandable that it should provide detailed information about Polyquad, the preservative contained therein. As stated above, a presentation on Polyquad was given at the last sales meeting during discussions about Systane.

5 **Email from a sales representative,** 'asking how to answer a formulary pharmacist'.

Alcon stated that this request related to the approved 'in-use life' of Systane, an ocular lubricant preserved with Polyquad, which was 60 days, compared with the 28 day 'in-use life' that applied to most eye drops; it did not relate to Travatan. The complainant's mistake in this regard indicated either their lack of understanding or the mischievous nature of their complaint.

6 **Email from Alcon** 'which asked representatives to no longer promote BAK-free as there had been a complaint from the ABPI.'

Alcon stated that the email in question (a copy was provided) was sent on 24 November to all sales teams after Alcon was notified of the complaint. There was no mention of the ABPI in the email and nor were representatives asked 'to no longer promote BAK-free' as alleged. This would have made no sense, since, as clarified above, they had never been told to promote the reformulated Travatan but had simply been instructed that they could inform customers of its regulatory status, if asked. However, in view of the possibility of further misinterpretation of Alcon's actions, it seemed appropriate to instruct representatives to refrain from even this very limited activity and to 'ensure that there are absolutely no conversations regarding this product until we have a product licence'.

This step was therefore taken purely to ensure that there could be no further misunderstanding of Alcon's promotional objectives and selling focus either internally or externally.

The Authority requested that Alcon send certain information, as part of its response, as listed below.

- Copies of all emails sent by the complainant's manager to his team about Travatan BAK free.

There were no such emails.

- Copies of representatives' call notes from his area, which refered to Travatan BAK-free.

  As stated earlier, Alcon had reviewed 3,552 call records for the period concerned from the ten representatives who reported to him. Forty of those reports either mentioned 'Travatan BAK-free' or the words 'BAK-free' directly linked to promotion of Travatan, 55% of which related to one person. Full details of those reports were provided. In Alcon's view, this number of reports and the nature of the reports concerned, was entirely consistent with the promotional activity outlined above and was not consistent with 'active promotion' of reformulated Travatan before the grant of a marketing authorization, as alleged.

- Copies of all representatives' briefing materials (including emails) which referred to Travatan BAK-free.

There were no such materials, with the exception of the slide set that was provided, a copy of which was not given to the representatives.

Summary and Conclusions

- The allegation had been made by an employee of Alcon who was dismissed due to failure to adhere to company procedures and might be vindictive or mischievous in nature.
- No substantial evidence was provided, or was available, to support the allegation.
- The benefits of Polyquad in patients with ocular surface disease (including glaucoma patients) were discussed. However, this was directly linked to Systane and not to Travatan.
- Representatives were permitted to confirm the impending availability of a reformulated Travatan in the two months before the marketing authorization was obtained, but only in response to a direct enquiry, in line with the requirements of the Code.
- At the first sign that Alcon's promotional activity might be misinterpreted or that some representatives might have deviated from their instructions (a communication from a competitor company), Alcon reinforced, to its representatives, the importance of complying with the Code.

In view of the above and the lack of any substantial evidence provided to support the allegation, Alcon denied any breach of Clauses 2, 3.1, 9.1 or 15.9.

In response to a request for further information, Alcon explained that the original marketing authorization for Travatan 40 micrograms/ml eye drops, solution was granted in November 2001. Since then, a number of variations had been filed to update the dossier, the last of which proposed an excipient change from BAK to Polyquad. This variation was formally approved by the European Commission on 29 November 2010. Therefore, the regulatory status of Travatan from the beginning of October through to 24 November 2010 was that the approved

formulation contained BAK.

As described above, the licence had been approved for over 10 years and it was only the status of the variation to this product licence, proposing the change in an excipient, that was referred to in an email to the representatives. Therefore, Alcon submitted that Travatan (preserved with BAK) and Travatan (preserved with Polyquad – so called 'BAK-free') were one and the same marketing authorization.

Alcon provided copies of the summary of product characteristics (SPC) for Travatan before and after the approval of the variation.

PANEL RULING

The Panel noted that when it received the complaint Travatan preserved with Polyquad was still the subject of a product licence variation. The formulation for which Alcon held a licence at that time was Travatan preserved with BAK. At a meeting held on 30 September/1 October, representatives were briefed on the revised formulation. In the last slide they were instructed that if ophthalmologists asked them about BAK-free Travatan they were to 'Explain that Alcon will introduce (within the new year) NEW Travatan BAK FREE soon, and explain that the new formulation has proven to be as powerful as the existing Travatan but with a better tolerability profile'. The Panel noted that this instruction went beyond Alcon's submission to the Authority that representatives could simply inform customers of the regulatory status of BAK-free Travatan if asked. The Panel noted Alcon's implied submission that replies made in response to individual enquiries from members of the health professions and appropriate administrative staff were not considered to be promotion. The Panel further noted, however, that to take the benefit of not being seen as promotion, such replies had to be in response to an unsolicited enquiry, relate solely to the subject matter of that enquiry, be accurate and not be misleading and not be promotional in nature. In that regard the Panel did not consider that the answer suggested by Alcon which referred to the efficacy and tolerability of a product, in response to a general enquiry about BAK-free Travatan could take the benefit of that exemption. In the Panel's view the suggested answer promoted BAK-free Travatan.

The Panel noted that as a result of this complaint, Alcon emailed its representatives on 24 November and asked them to ensure that there were absolutely no conversations about Travatan BAK-free until it had a product licence. An analysis of the call records from one region showed that one representative in particular regularly referred to BAK-free Travatan from early October until early November. A typical entry by that individual read 'Briefly mentioned Travatan in terms of absolute IOP [intra-ocular pressure] drop, control of diurnal fluctuations, tolerability, price and future BAK free formulation'. It appeared from the call notes that any discussion about BAK-free Travatan had been initiated by the representative and not a health professional. In that regard the Panel noted Alcon's submission that the content of call notes was often not scrutinised in detail and that any indication that a representative had not adhered to company policy might not be picked up at the time unless the practice was widespread. The Panel was concerned about the company's approach which it considered was unacceptable.

The Panel noted that Alcon's product, Systane (a device), was an ocular lubricant preserved with Polyquad and could be promoted. Representatives were instructed to reinforce the message that Systane did not contain BAK, that BAK was associated with ocular surface toxicity and that Polyquad did not exhibit the same ocular surface toxicity as BAK. Representatives were also encouraged to use the promotion of Systane to raise the subject of dry eye in glaucoma patients and its potential link to the presence of BAK in eye drops used for treatment and to assess the level of interest in this topic to assist targeting of future sales activity. In the Panel's view it was likely that the discussion of Systane and problems of dry eye in glaucoma would solicit questions about BAK-free treatments for the condition.

The Panel considered that, on the balance of probabilities, Alcon representatives had promoted BAK-free Travatan before the grant of a marketing authorization which permitted the sale or supply of that formulation. A breach of Clause 3.1 was ruled.

The Panel further considered that the presentation used to brief the representatives in September/October, which encouraged them to discuss and make claims for Travatan BAK-free, advocated a course of action which was likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel, however, did not consider that the activity was such as to bring discredit upon the industry and no breach of Clause 2 was ruled.

Complaint received **24 November 2010**

Case completed **14 March 2011**

CASE AUTH/2373/11/10

DOCTOR v SANOFI-AVENTIS

Special report in journal

A doctor complained about a four page 'special report' on atrial fibrillation which appeared on pages 17-20 of the Health Service Journal (HSJ), 25 November 2010. The top right hand corner of the first page of the report (page 17 of the HSJ) featured a prominent Sanofi-Aventis company logo and, in smaller type, the statement 'This special report is paid for and sponsored by Sanofi-Aventis. Sanofi-Aventis have had no editorial input'.

The complainant noted that the supplementary information to the Code stated that, 'When a company pays for, or otherwise secures or arranges the publication of promotional material in journals, such material must not resemble independent editorial material'. The complainant alleged that the material was promotional because Sanofi-Aventis' new medicine dronedarone [Multaq] was favourably mentioned several times. The editorial style of the special report was extremely similar or identical to that of the HSJ with regard to, *inter alia*, page layout, typeface, font size, colour scheme and number of columns. The complainant submitted that a reader flicking through the journal, especially from back to front, could read pages 18-20 and not know that Sanofi-Aventis had secured publication.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The special report in question had been paid for and sponsored by Sanofi-Aventis; it had been initiated as a result of a discussion between the HSJ and Sanofi-Aventis' communications agency. The agency had facilitated contact between the HSJ and the clinical and non-clinical experts who provided their input. An email from the agency to the HSJ referred to working with the HSJ to produce a special report and with one of the expert contributors quoted in the special report and listed the key topics that would be covered. The author of the email thanked the HSJ for its patience in '… getting this off the ground'. Sanofi-Aventis stated that it could check the final text for factual inaccuracies. The Panel noted Sanofi-Aventis' submission that the layout of the piece was chosen by the HSJ to maintain continuity with the rest of the journal.

The top right hand corner of the front cover of the HSJ at issue listed three articles within, one of which was 'Improving cardiac care special report: 17'. The way in which the special report was listed was indistinguishable from the other two articles. There was no reference on the front cover to Sanofi-Aventis' involvement in the special report. The special report contained several positive mentions of dronedarone. In the Panel's view, although other medicines were mentioned, the balance of the piece was in favour of dronedarone.

The Panel considered that Sanofi-Aventis had, through its communications agency, influenced the scope and content of the special report and facilitated contact with clinical and non-clinical experts. In that regard the Panel considered that there was no strictly arm's length arrangement between the provision of sponsorship and the generation of the special report. In the Panel's view, Sanofi-Aventis was inextricably linked to the production of the report and given its content and presentation the report was, in effect, disguised promotional material for dronedarone. The report was not easily distinguished from the editorial content of the HSJ and its content appeared to be wholly independent of Sanofi-Aventis which was not so. A breach of the Code was ruled.

A doctor complained about a four page 'special report' about atrial fibrillation which appeared on pages 17-20 of the Health Service Journal (HSJ), 25 November 2010. The top right hand corner of the first page of the report (page 17 of the HSJ) featured a prominent Sanofi-Aventis company logo and, in smaller type, the statement 'This special report is paid for and sponsored by Sanofi-Aventis. Sanofi-Aventis have had no editorial input'.

COMPLAINT

The complainant noted that the supplementary information to Clause 12.1 of the Code stated that, 'When a company pays for, or otherwise secures or arranges the publication of promotional material in journals, such material must not resemble independent editorial material'. The complainant further noted that Sanofi-Aventis acknowledged that it 'paid for and sponsored' the material. The complainant alleged a breach of Clause 12.1. The material was promotional because Sanofi-Aventis'

new medicine dronedarone [Multaq] was favourably mentioned at least seven times, with no reference to side-effects or safety concerns. The editorial style of the special report was extremely similar or identical to the standard editorial text of the HSJ with regard to page layout, typeface, font, font size, colour scheme, number of columns, text boxes, call-outs etc. The complainant submitted that a reader flicking through the journal, especially from back to front, could read pages 18-20 and not know that Sanofi-Aventis had secured publication.

RESPONSE

Sanofi-Aventis explained that the 'special report' was a regular feature of the HSJ and appeared in the body of the journal itself rather than as a separate supplement. It was not a promotional piece but rather an independent, educational piece written by the HSJ.

The declaration and sponsorship statement was clearly visible at the outset of the article (page 17) and Sanofi-Aventis had had no editorial input into the report.

The article was written by an HSJ employee and included comments from clinicians and non-clinicians. Atrial fibrillation was of interest to the NHS due to its impact on patients and the NHS as a whole. Given the heritage, current interest and breadth of research that Sanofi-Aventis had carried out in this disease area, it seemed appropriate for the company to support the special report at issue.

Sanofi-Aventis submitted that although the article initially focussed on the cost impact of atrial fibrillation on the NHS it also discussed the overall management of the disease. Many different treatments, both pharmacological and non-pharmacological (such as ablation) were referred to and of the pharmacological treatments mentioned, many classes (eg beta-blockers, calcium channel blockers) and individual medicines (eg aspirin, warfarin, digoxin, amiodarone, dabigatran) other than dronedarone were named. Given that dronedarone was a new treatment option in this disease area, it seemed only logical that it was referred to in the article, either in the author's text or in the comments from the contributing experts. While the side-effects of dronedarone were not mentioned, this was also the case for all the other medicines and classes of medicines that were named.

The layout of the article was not within the control of Sanofi-Aventis. While the company had paid for and sponsored the article, its involvement in the content went no further, other than the opportunity to check the text for factual inaccuracies which it was permitted to point out to the author. The layout of the piece, such as the typeface or font size, was chosen by the HSJ so as to maintain continuity with the rest of the journal.

Sanofi-Aventis noted that the complainant had alleged a breach of Clause 12.1 and referred to supplementary information in the Code which stated that 'When a company pays for, or otherwise secures or arranges the publication of promotional material in journals, such material must not resemble independent editorial matter'. The article did not promote the prescription, supply, sale or administration of a medicine, and was therefore, by definition, not promotional. The article was authored by an HSJ employee and Sanofi-Aventis did not, as stated clearly at the outset of the special report, have any editorial input. As such, this was not disguised promotional material as it was independent editorial matter. Sanofi-Aventis denied a breach of Clause 12.1.

In response to a request for further information, Sanofi-Aventis stated that the article in question was initiated as a result of discussion between the HSJ and Sanofi-Aventis' communications agency at the time. As such, there was no formal agreement in place between Sanofi-Aventis and the HSJ as limited involvement in the article was anticipated.

Sanofi-Aventis had made no use of the article in promotional activities.

In response to a further request for more information, Sanofi-Aventis explained that communication with the HSJ regarding the article was carried out by its communications agency and not by Sanofi-Aventis itself. There was no formal agreement in place between the communications agency and the HSJ as the article was to be written by an HSJ employee. The article was written following her discussions with the experts who were quoted in the piece. The communications agency helped by facilitating contact between the HSJ and clinical and non-clinical experts who provided their input.

Most of the communication between the HSJ and the communications agency was by telephone or in person, which limited the documentation. Sanofi-Aventis provided an email trail between the HSJ and the communications agency in which, it submitted, the key themes were the logistics of facilitating contact between the HSJ and the contributing experts. The emails demonstrated that the article was never intended to be promotional, hence the lack of briefing material.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company

and no use by the company of the material for promotional purposes.

The special report in question had been paid for and sponsored by Sanofi-Aventis. The report had been initiated as a result of a discussion between the HSJ and Sanofi-Aventis' then communications agency. The communications agency had helped by facilitating contact between the HSJ and the clinical and non-clinical experts who provided their input. An email from the agency to the HSJ referred to working with the HSJ to produce a special report and with one of the expert contributors quoted in the special report. This email also listed the key topics that would be covered in the article. The author of the email thanked the HSJ for its patience in '… getting this off the ground'. Sanofi-Aventis stated that it could check the final text for factual inaccuracies which it could point out to the author. The Panel noted Sanofi-Aventis' submission that the layout of the piece was chosen by the HSJ to maintain continuity with the rest of the journal.

The top right hand corner of the front cover of the HSJ at issue listed three articles within, one of which was 'Improving cardiac care special report: 17'. The way in which the special report was listed was indistinguishable from the other two articles. There was no reference on the front cover to Sanofi-Aventis' involvement in the special report. The special report contained several positive mentions of dronedarone. In the Panel's view, although other medicines were mentioned, the balance of the piece was in favour of dronedarone.

The Panel considered that Sanofi-Aventis had, through its communications agency, influenced the scope and content of the special report and facilitated contact with clinical and non-clinical experts. In that regard the Panel considered that there was no strictly arm's length arrangement between the provision of sponsorship and the generation of the special report. In the Panel's view, Sanofi-Aventis was inextricably linked to the production of the report and given its content the report was, in effect, promotional material for dronedarone. The Panel considered that it was disguised promotion; the presentation of the report was such that it was not easily distinguished from the editorial content of the HSJ and the content of the report itself appeared to be wholly independent of Sanofi-Aventis which was not so. A breach of Clause 12.1 was ruled.

Complaint received **29 November 2010**

Case completed **8 March 2011**

CASE AUTH/2377/12/10

NOVO NORDISK v MERCK SHARP & DOHME

Promotion of Janumet

Novo Nordisk complained about one screen of an e-detail for Janumet (sitagliptin and metformin) produced by Merck Sharp & Dohme. The top of the screen featured a coloured band with the Janumet product logo in the top left hand corner. Below the band was the headline 'Powerful HbA_{1c} reductions helps more patients get to goal'. The screen depicted data showing the decrease in HbA_{1c} as reported by Raz *et al* (2008).

Novo Nordisk alleged that the heading contained a hanging comparison. 'More patients' compared to what? The clinical trial data compared sitagliptin (added to metformin) with placebo (added to metformin). Therefore the headline should state that the HbA_{1c} reduction induced by sitagliptin helped more people to achieve glycaemic target than the HbA_{1c} reduction achieved with placebo. Readers were likely to interpret the claim to mean that sitagliptin helped more patients to get to goal than other antihyperglycaemic treatments, which was not so. Thus the headline was misleading and could not be substantiated by the cited study, Raz *et al*.

Although the headline suggested that more patients got to goal, there was no mention of the proportion of patients who reached the target, nor was the goal itself clarified. A secondary endpoint in Raz *et al* was the proportion of patients who achieved the therapeutic goal of HbA_{1c} <7%. In context of the headline, the exact proportion of patients who got to goal was an essential piece of information. There was no doubt that a placebo-corrected 1% HbA_{1c} reduction looked more attractive than the observed rates of 22.1% (week 18) or 13.7% (week 30) which were the proportions of sitagliptin-treated patients who reached the <7% HbA_{1c} target. Putting this hidden 22.1/13.7% rates in the correct context, the readers should also have been informed that these rates were only numerically greater than the observed rate in the placebo arm. Raz *et al* suggested that there was no statistically significant difference between the two treatments in this regard. Novo Nordisk believed these were the reasons why Merck Sharp & Dohme did not report the actual outcome.

Novo Nordisk noted that the current type 2 diabetes clinical treatment recommendation from the National Institute for health and Clinical Excellence (NICE), set the target HbA_{1c} at 6.5% for the stage of diabetes which was investigated in Raz *et al* (second line oral anti-diabetic treatment). Since Raz *et al* had set the target HbA_{1c} as <7%, Novo Nordisk believed this must be clarified in the e-detail. The higher HbA_{1c} target defined in Raz *et al*, compared to the general UK recommendation, meant that the proportion of patients who achieved the UK relevant HbA_{1c} target of 6.5% would have been even smaller than the 22.1/13.7% reported in Raz *et al* in relation to the <7% target.

On the basis of the above, Novo Nordisk alleged that in the context in which it appeared, the headline was misleading and could not be substantiated.

Finally on the same screen, Novo Nordisk alleged that undue emphasis was placed on an HbA_{1c} drop of 1.8% in a subgroup of 20% (n=19) of patients from the sitagliptin group. Merck Sharp & Dohme had failed to highlight that this improvement was not statistically different from the HbA_{1c} drop observed in the placebo group, at least this was suggested by the authors who stated, 'Numerically greater HbA_{1c} reductions from baseline were observed in sitagliptin-treated patients with higher baseline HbA_{1c} values'.

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

The Panel noted that Raz *et al* had evaluated the efficacy and safety of sitagliptin as an add-on to metformin therapy in patients with moderately severe type 2 diabetes (HbA_{1c} ≥ 8% and ≤11%). The primary efficacy endpoint was the reduction in HbA_{1c} at 30 weeks. The proportion of patients meeting the goal of HbA_{1c} <7% was also analysed.

The Panel considered that the headline 'Powerful HbA_{1c} reductions help more patients get to goal' was a claim for Januvia. The claim begged the question 'More patients than what?'. In that regard the Panel considered that the claim was a hanging comparison and as such it was not capable of substantiation. Breaches of the Code were ruled.

The Panel noted that no screen in the e-detail defined what the goal HbA_{1c} was. Raz *et al* had set a goal of < 7% although the NICE guidelines recommended a general target of ≤ 6.5% for patients on one glucose-lowering medicine. The Panel considered that with no numerical value of the goal in question, the material was not sufficiently complete such as to enable readers to form their own opinion of the therapeutic value of the medicine. In that regard the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

The Panel noted that the study protocol pre-specified subgroups of patients according to baseline HbA_{1c}. Results showed that the higher a patient's baseline HbA_{1c}, the greater the fall in HbA_{1c} with sitagliptin therapy. In the subgroup with the highest baseline HbA_{1c} (≥ 10% n=20) the net

reduction in HbA_{1c} with sitagliptin therapy was 1.8% at week 18 and 1.4% at week 30. The smaller placebo-adjusted decrease at week 30 was due to a drop in HbA_{1c} in the placebo (metformin only) group, not a loss of glycaemic control in the sitagliptin group.

The Panel questioned whether the high baseline group was large enough for the results to be definitive. Merck Sharp & Dohme stated that a statistical analysis had not been undertaken but that in its view the reductions were clinically significant. Although the results appeared to support the view that the magnitude of the fall in HbA_{1c} from baseline was likely to be proportional to the baseline HbA_{1c}, the Panel did not consider that a definitive claim for a 1.8% reduction could be made based on the results from the small subgroup. The Panel further noted that the difference between placebo and sitagliptin narrowed at week 30 such that the difference between the two was only 1.4% (due to an improvement in the placebo group). Overall, the Panel considered that the 18 week results of the subgroup had been over emphasised. The figure of -1.8% appeared on a prominent downward pointing white arrow which was within a bright pink circle. The reader's eye would be drawn to the data which, in the Panel's view, was not based on a sufficiently robust dataset for such a claim. In that regard the Panel considered that the claim was misleading. Breaches of the Code were ruled which were appealed by Merck Sharp & Dohme.

The Appeal Board noted that Raz *et al* had assumed a within-group standard deviation of 1% for measuring HbA_{1c} and that approximately 86 patients per treatment group would provide 90% power to detect a true between-group difference of 0.5% in the mean change in HbA_{1c} from baseline.

The background colour of the e-detail screen at issue was mid blue and to the right of centre was a light blue box showing the placebo adjusted median change in HbA_{1c} from baseline when sitagliptin 100mg once daily was added to metformin therapy (n=95). A mid blue downward arrow showed a fall of 1% ($p<0.001$ vs placebo). To the right of the light blue box a prominent downward white arrow within a bright pink circle depicted a 1.8% placebo adjusted additional reduction in HbA_{1c} from baseline after 18 weeks in the subgroup of patients (n=19) with a baseline $HbA_{1c} \geq 10\%$.

The Appeal Board noted that both sets of data appeared prominently on the e-detail page but that only the results from the larger group had been subject to statistical analysis. Given the visual prominence of the downward white arrow, however, the Appeal Board considered that the reader would be drawn to the data from the high baseline group and would assume that it was as statistically robust as the data from the whole group, which was not so. The study was not powered to detect a difference in such a small group and in that regard the Appeal Board noted that the authors had stated that 'patients with higher baseline HbA_{1c} also *trended* towards larger reductions in HbA_{1c}' (emphasis added).

The Appeal Board considered that the results from the high baseline HbA_{1c} group had been over emphasised and in that regard the presentation of the data in the e-detail was misleading and did not accurately reflect Raz *et al*. The Appeal Board upheld the Panel's rulings of breaches of the Code. The appeal on this point was thus unsuccessful.

Novo Nordisk Limited complained about screen 7 of an e-detail (ref 02-11 JMT.10.GB.37010.AV) for Janumet (sitagliptin and metformin) produced by Merck Sharp & Dohme Limited. The top of the screen featured a coloured band with the Janumet product logo in the top left hand corner. Below the band was the headline 'Powerful HbA_{1c} reductions helps more patients get to goal'. The screen depicted data showing the decrease in HbA_{1c} as reported by Raz *et al* (2008). Novo Nordisk stated that inter-company dialogue had failed to resolve the matter. Merck Sharp & Dohme stated that the complaint was its first intimation that Novo Nordisk was dissatisfied with its response.

COMPLAINT

Novo Nordisk alleged that the heading contained a hanging comparison. 'More patients' compared to what? The clinical trial data detailed compared sitagliptin (added to metformin) with placebo (added to metformin). Therefore the headline should state that the HbA_{1c} reduction induced by sitagliptin helped more people to achieve glycaemic target than the HbA_{1c} reduction achieved with placebo which was correctly stated in the efficacy results part of the paper ('Compared to placebo, sitagliptin significantly increased the probability of achieving the HbA_{1c} goal of 7.0% …'). Since physicians relatively rarely treated patients with placebo, readers were likely to interpret the claim to mean that sitagliptin helped more patients to get to goal than other antihyperglycaemic treatments, which was not so. Thus the headline was misleading and could not be substantiated by the cited study, Raz *et al*, in breach of Clauses 7.2 and 7.4 of the Code.

Although the headline suggested that more patients got to goal, there was no mention on the screen about the proportion of patients who reached the target during the trial, nor was the goal itself clarified. A secondary efficacy endpoint in Raz *et al* was the proportion of patients who achieved the therapeutic goal of HbA_{1c} <7%. In context of the headline, the exact proportion of patients who got to goal was an essential piece of information for the readers. There was no doubt that a placebo-corrected 1% HbA_{1c} reduction looked more attractive for most clinicians than the observed rates of 22.1% (week 18) or 13.7% (week 30) which were the proportions of sitagliptin-treated patients who reached the <7% HbA_{1c} target. Putting this hidden 22.1/13.7% rates in the correct context, the readers should also have been informed that these

rates were only numerically greater than the observed rate in the placebo arm. This wording from Raz *et al* suggested that there was no statistically significant difference between the two treatments in this regard. Novo Nordisk believed these were the reasons why Merck Sharp & Dohme did not report the actual outcome to which it referred in the screen's headline.

Similarly, the therapeutic goal must have been defined since publication by the National Institute for health and Clinical Excellence (NICE) of the current type 2 diabetes clinical treatment recommendation, which was undoubtedly the most relevant UK clinical guideline and which set this target as 6.5% in general at the stage of diabetes which was investigated in Raz *et al* (second line oral anti-diabetic treatment). Since Raz *et al* had set the target HbA_{1c} as <7%, Novo Nordisk believed this must be clarified in the e-detail. The higher HbA_{1c} target defined in Raz *et al*, compared to the general UK recommendation, meant that the proportion of patients who achieved the UK relevant HbA_{1c} target of 6.5% would have been even smaller than the 22.1/13.7% which were reported in Raz *et al* in relation to the <7% target.

On the basis of the above, Novo Nordisk alleged that in the context in which it appeared, the headline was misleading in breach of Clause 7.2 and could not be substantiated, in breach of Clause 7.4.

Finally on the same screen, Novo Nordisk alleged that undue emphasis was placed on an HbA_{1c} drop of 1.8% in a subgroup of 19 patients from the sitagliptin group (only 20% of the sitagliptin patients). Merck Sharp & Dohme had failed to highlight that this improvement was not statistically different from the HbA_{1c} drop observed in the placebo group, at least this was suggested by the authors who stated, 'Numerically greater HbA_{1c} reductions from baseline were observed in sitagliptin-treated patients with higher baseline HbA_{1c} values'. Novo Nordisk alleged that the exaggeration of the statistically non-significant subgroup finding was in breach of Clauses 7.2 and 7.3.

RESPONSE

Merck Sharp & Dohme noted that on the screen in question, underneath the general headline 'Powerful HbA_{1c} reductions help more patients get to goal', details were given of the HbA_{1c} reductions seen when sitagliptin was added to metformin therapy vs placebo (Raz *et al*). No data were given on this screen (or on any other screen in the e-detail) about the relative proportions of patients achieving goal in Raz *et al*. Despite this, the complaint focused on the latter.

The two questions prompted by the first part of Novo Nordisk's complaint could be summarised as follows: Did the headline contain a hanging comparison within the meaning of the Code? And did the copy at least imply that a higher proportion of patients achieved treatment goal in the sitagliptin arm; and, if so, was this implication justified?

Concerning the headline, no specific product was mentioned. Merck Sharp & Dohme believed that the statement in question merely drew attention to the self-evident relationship between reductions in HbA_{1c} and attainment of goal a statement exemplified as far as sitagliptin was concerned by the data that followed. In effect, it stated that any agent that provided powerful HbA_{1c} reductions would be expected, almost by definition, to lead to an increased proportion of patients achieving goal, however defined. The remainder of the copy on the screen sought to answer the question as to whether sitagliptin provided such powerful HbA_{1c} reductions. As such, Merck Sharp & Dohme did not believe that the headline could possibly be interpreted as a hanging comparison within the meaning of the Code.

As noted above, the screen in question did not contain any data relating to the attainment of goal in Raz *et al*. Nevertheless, Merck Sharp & Dohme accepted that the headline could imply that sitagliptin led to a greater proportion of patients achieving goal in this study. Was that justified? Merck Sharp & Dohme maintained that it was. Raz *et al* contained the statement 'Compared with placebo, sitagliptin significantly increased the probability of achieving the HbA_{1c} goal of <7.0% at both week 18 and week 30 ($p=0.012$ and $p<0.001$, respectively)'. Thus, even if the copy had explicitly claimed an improvement in attainment of goal with sitagliptin, that claim would have been accurate and substantiated by Raz *et al*. Even in such a case, there was no obligation under the Code to include every detail of the data, provided that the claim was justified; Merck Sharp & Dohme stated that in any event no such explicit claim was made in the e-detail.

Merck Sharp & Dohme considered that Novo Nordisk's assertion that it was inadmissible to provide attainment-of-goal data vs placebo to be preposterous, and all the more so in that the data Novo Nordisk complained about were not included in the e-detail in the first place. Furthermore the phrase 'numerically greater', taken from Raz *et al* and cited in the complaint, referred to the increase in the number of patients achieving goal from week 18 to week 30 within the sitagliptin arm. It did not refer to the differences between the sitagliptin and placebo arms, which were indeed statistically significant, as evidenced by the quotation in the paragraph above. Finally, the target of 7% for HbA_{1c} goal was pre-specified in the trial protocol and was widely accepted as reasonable by the diabetological community.

Merck Sharp & Dohme did not accept that undue emphasis had been placed on the increased HbA_{1c} reduction in Raz *et al* in higher-baseline patients. Rather, the data was placed in context with the findings from the main part of the study. There was a well-recognised relationship between baseline HbA_{1c} and the magnitude of the HbA_{1c} reduction

with therapeutic agents (Bloomgarden *et al* 2006), and the higher-baseline data from Raz *et al* was thus relevant to potential prescribers. The subgroup analysis in Raz *et al* was pre-specified in the study protocol and as was usual in such analyses, no formal statistical analysis was done on the data, and Merck Sharp & Dohme did not suggest otherwise in the e-detail. Nevertheless, noted in inter-company correspondence - the reductions were clinically significant and the error bars in the graph in Figure 4 in Raz *et al* were widely separated. Finally, Merck Sharp & Dohme noted that it included all relevant data for this higher-baseline analysis in the e-detail, including placebo-adjusted figures, n-numbers and figures for both relevant time-points. It was difficult to see how it could have presented these data any more openly or transparently.

In conclusion, Merck Sharp & Dohme denied the alleged breaches of Clauses 7.2, 7.3 and 7.4.

In inter-company correspondence, Merck Sharp & Dohme stated that if the headline 'Powerful HbA_{1c} reductions help more patients get to goal' was interpreted as a claim for sitagliptin, it only stated that sitagliptin was effective, and that using it could be expected to lead to a greater proportion of patients reaching their treatment goal than would otherwise be the case. This was not equivalent to stating that sitagliptin was 'better' or 'stronger', which were true hanging comparisons. As such, Merck Sharp & Dohme believed that the headline was acceptable and its meaning was made abundantly clear by the context in which it appeared.

Merck Sharp & Dohme was also mystified by Novo Nordisk's assertion that the headline could be considered misleading. In Raz *et al* it was clearly stated that 'Compared with placebo, sitagliptin significantly increased the probability of achieving the HbA_{1c} goal of <7.0% at both week 18 and week 30 ($p=0.012$ and $p<0.001$, respectively)'. Given that the claim was therefore accurate and substantiable, Merck Sharp & Dohme did not understand how it could be considered misleading.

Merck Sharp & Dohme also did not accept the assertion that it was inappropriate or misleading to follow a claim that mentioned attainment of goal with absolute HbA_{1c} reduction data. As noted above, there was a self evident connection between the two, a connection that was made explicit in the headline to the screen in question. Furthermore, given that figures such as 7% were guidelines only, and that ideally treatment goals should be individualised to suit a patient's particular circumstances, it was as useful for potential prescribers to understand the absolute HbA_{1c} reductions that might be expected from an antidiabetic medicine as it was for them to know the proportions of patients attaining an HbA_{1c} goal.

It appeared that Novo Nordisk's concerns about the HbA_{1c} reductions in higher-baseline patients were based on a misinterpretation of Raz *et al*; the company appeared to believe that the 1.8% and 1.4% figures referred to non-placebo-adjusted and placebo-adjusted HbA_{1c} reductions in higher-baseline patients at the same time-point. This was not so as made clear in Figure 4 in the paper. Both figures were placebo-adjusted. The 1.8% figure was the reduction at week 18 and the 1.4% figure that at week 30. The pre-specified primary end-point of the trial was the HbA_{1c} reduction at week 18 and so 1.8% represented the 'official' result as far as higher-baseline patients were concerned. As noted in Raz *et al*, and in the e-detail, there was an improvement in HbA_{1c} in the placebo group from week 18, which resulted in a placebo-adjusted difference of 1.4% at week 30. In the interests of transparency, both figures were included in the e-detail.

Merck Sharp & Dohme did not understand why Novo Nordisk considered that these differences were not statistically significant as no formal statistical analysis was performed on the figures (as was normally the case with subgroup data of this nature). That said, the graphs in Figure 4 showed that the error bars for the sitagliptin and placebo reductions did not overlap by a considerable margin; in any event the reductions were undeniably clinically significant. The sentence from Raz *et al* quoted by Novo Nordisk referred to changes from baseline within the sitagliptin-treated group and not to differences with respect to placebo.

In summary, the sub-analysis of the higher-baseline patients was pre-specified in the study protocol, the HbA_{1c} reductions given in the e-detail were placebo-adjusted, figures were given for both relevant time-points and the text included both n-numbers and an explanation for the change in the differential reduction from week 18 to week 30. It was difficult to see how Merck Sharp & Dohme could have been any more open and transparent in representing these data.

Finally, Merck Sharp & Dohme noted that although 96 patients were randomised to receive sitagliptin, HbA_{1c} data were finally available for 95, as noted in Table 2 in Raz *et al*.

PANEL RULING

The Panel disagreed with Merck Sharp & Dohme's submission that the headline 'Powerful HbA_{1c} reductions help more patients get to goal' was a statement of the self-evident relationship between reductions in HbA_{1c} and attainment of goal and not a claim for sitagliptin. In the context of an e-detail for Januvia, and appearing beneath the product logo, the Panel considered that the headline would be read as a claim for that product.

The Panel noted that Raz *et al* had evaluated the efficacy and safety of sitagliptin as an add-on to metformin therapy in patients with moderately severe type 2 diabetes ($HbA_{1c} \geq 8\%$ and $\leq 11\%$). The primary efficacy endpoint was the reduction in HbA_{1c} at 30 weeks. The proportion of patients meeting the goal of HbA_{1c} <7% was also analysed.

The Panel considered that the headline 'Powerful HbA_{1c} reductions help more patients get to goal' was a claim for Januvia. The claim begged the question 'More patients than what?'. In that regard the Panel considered that the claim was a hanging comparison and as such it was not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that neither the screen at issue nor any other screen in the e-detail defined what the goal HbA_{1c} was. Raz *et al* had set a goal of < 7% although the NICE guidelines recommended a general target of ≤ 6.5% for patients on one glucose-lowering medicine. The Panel considered that with no reference as to the numerical value of the goal in question, the material was not sufficiently complete such as to enable readers to form their own opinion of the therapeutic value of the medicine. In that regard the claim was misleading and a breach of Clause 7.2 was ruled. The Panel further considered that the claim could not be substantiated. A breach of Clause 7.4 was ruled.

The Panel noted that the study protocol pre-specified that subgroups of patients would be analysed for changes from baseline HbA_{1c} at weeks 18 and 30 to evaluate prescribing factors that could potentially influence treatment outcome. One of the subgroups was defined by baseline HbA_{1c} and results showed that the higher a patient's baseline HbA_{1c}, the greater the fall in HbA_{1c} with sitagliptin therapy. In the subgroup with the highest baseline HbA_{1c} (≥ 10% n=20) the net reduction in HbA_{1c} with sitagliptin therapy was 1.8% at week 18 and 1.4% at week 30. The smaller placebo-adjusted decrease at week 30 was due to a drop in HbA_{1c} in the placebo (metformin only) group, not a loss of glycaemic control in the sitagliptin group.

The Panel noted that according to Raz *et al* there were only 20 patients in the sitagliptin group (the e-detail stated 19 patients) with a baseline HbA_{1c} ≥ 10% and in that regard it questioned whether the group was large enough for the results to be definitive. Merck Sharp & Dohme stated that a statistical analysis had not been undertaken but that in its view the reductions were clinically significant. Although the results appeared to support the view that the magnitude of the fall in HbA1c from baseline was likely to be proportional to the baseline HbA_{1c}, the Panel did not consider that a definitive claim for a 1.8% reduction could be made based on the results from the small subgroup in Raz *et al*. The Panel further noted that the difference between placebo and sitagliptin narrowed at week 30 such that the difference between the two was only 1.4% (due to an improvement in the placebo group). Overall, the Panel considered that the 18 week results of the subgroup had been over emphasised. The figure of -1.8% appeared on a prominent downward pointing white arrow which was within a bright pink circle. The reader's eye would be drawn to the data which, in the Panel's view, was not based on a sufficiently robust dataset for such a claim. In that regard the Panel considered that the claim was misleading. Breaches of Clauses 7.2 and 7.3 were ruled which were appealed by Merck Sharp & Dohme.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme noted that Janumet was a fixed-dose combination of metformin and sitagliptin for the treatment of appropriate patients with type 2 diabetes. The screen in question presented data from Raz *et al*. In addition to text summarising the results of the study, the screen depicted in diagrams the mean reduction in HbA_{1c} of 1% obtained in the combination-treated group relative to placebo at 18 weeks (the scheduled end-point of the main trial) and the greater reduction of 1.8% seen in a high-baseline group (initial HbA_{1c} ≥10%), also at 18 weeks. Additional explanatory text, including further data, was appended to both diagrams.

Merck Sharp & Dohme submitted that the basis of Novo Nordisk's complaint about these data was that the results in the high-baseline group had been overemphasised, and the Panel upheld that view and ruled breaches of Clauses 7.2 and 7.3.

Merck Sharp & Dohme submitted that the Panel's ruling of a breach of Clause 7.3 was technically in error. The data in question fell outside the scope of this clause, which dealt specifically with comparisons with competitor products. The data presented in the e-detail were non-comparative. Accordingly, Merck Sharp & Dohme submitted that there was no case to answer with respect to this clause, and the remainder of its submission was focussed on the ruling of a breach of Clause 7.2. Merck Sharp & Dohme did not consider that the presentation of the high-baseline data was misleading.

Merck Sharp & Dohme noted that the Panel was concerned with the physical presentation of the high-baseline data (colour and prominence), and with the robustness of the data itself. As any judgement on whether data had been overemphasised depended largely on the robustness, significance and generalisability of the data in question, Merck Sharp & Dohme dealt with this issue first.

Merck Sharp & Dohme submitted that before addressing the specifics of the data presented in the e-detail, it might be helpful to consider their relevance. There was a widely recognised relationship between the level of baseline glycaemia and the glycaemic reductions obtained with antidiabetic agents. This relationship was investigated in a meta-analysis for 'traditional' antidiabetic agents by Bloomgarden *et al* (2006) and updated by two of the same authors for the DPP4-inhibitor class of drugs (of which sitagliptin was a member) in a letter in the New England Journal of Medicine (Bloomgarden and Inzucchi 2007). Further meta-analyses had been published by Chapell *et al* (2009), comparing sitagliptin with thiazolidinediones; and by Phung *et al* (2010), looking at all classes of oral antidiabetic agents.

Merck Sharp & Dohme submitted that it was clear from the evidence above that the average reductions in glycaemia reported in trials with antidiabetic agents only told part of the story of an individual agent's potential efficacy. It was therefore of great relevance for prescribers to have an accurate idea of the sort of glycaemic reductions they might expect to see in patients of often widely differing baseline glycaemic status.

Turning to the data presented in the Janumet e-detail, Merck Sharp & Dohme submitted that it might be useful to examine it using the criteria of Clause 7.2 of the Code as a guide. Were the data accurate? Merck Sharp & Dohme did not believe that there was any dispute that the high-baseline data presented in the e-detail was an accurate reflection of the findings from the Raz *et al*. As a minor point, the Panel suggested that there was a discrepancy between the n=19 figure cited in the e-detail and the n=20 figure for the high-baseline subgroup cited in the original paper. However, a footnote to a table of data in Raz *et al* clearly stated that the subgroup contributed only 19 patients to the full-analysis-set population.

Merck Sharp & Dohme noted that there was a question as to whether the data were balanced, bearing in mind the subsequent provision of the clause that 'Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. As previously stated Merck Sharp & Dohme submitted that it had included every relevant piece of information in the piece that would enable a potential prescriber to draw a conclusion as to the significance of the data presented. The nature of the subgroup was clearly identified, as was the n-number, the fact that this was a placebo-adjusted figure, and the population set. The Panel drew attention to the additional information presented concerning the results obtained at 30 weeks, showing that – as a result of an improvement in glycaemic status in the placebo group – the placebo-subtracted reduction in HbA_{1c} had fallen to 1.4%. The planned end-point of the study was at 18 weeks, and that, if anything, including the 30-week extension data in the piece further demonstrated Merck Sharp & Dohme's commitment to providing appropriately balanced information. The company noted that the absolute (as opposed to placebo-adjusted) reduction with sitagliptin in this high-baseline group remained virtually unchanged from 18 to 30 weeks.

With regard to the data being fair and objective, Merck Sharp & Dohme submitted that at several points in its ruling, the Panel expressed concern that an n-number of 19 might not be considered large enough for the results to be definitive. Leaving aside the existence of additional supportive data obtained with sitagliptin (see below), it should be noted, firstly, that the figure of n=19 referred only to the number of patients in the high-baseline subgroup treated with active product. There were a further 13 patients in the high-baseline subgroup treated with placebo, giving a total n of 32 for the subgroup as a whole. It was this figure that was relevant in assessing the validity of a placebo-adjusted comparison. Raz *et al* demonstrated that, at both 18 and 30 weeks, there was very wide separation between the confidence intervals of the placebo- and sitagliptin-treated groups for all levels of baseline glycaemia, and particularly so for the baseline subgroup of 10% or above. This strongly suggested that the patient numbers involved were more than sufficient to demonstrate a significant difference between the two treatment groups.

Merck Sharp & Dohme also noted that, in assessing fairness and emphasis, the data related to the primary indication for which Janumet was licensed, ie improvement in glycaemia. Furthermore, the analysis of the high-baseline subgroup was not carried out post hoc, but was a pre-specified analysis in the study protocol.

Merck Sharp & Dohme noted that there was a question as to whether the data were 'based on an up-to-date evaluation of all the evidence' and did they 'reflect that evidence clearly'? Merck Sharp & Dohme submitted that the data from Raz *et al* about glycaemic reductions in higher-baseline patients was not an isolated clinical finding. On the contrary – in addition to the evidence from the meta-analyses referred to above – several individual clinical trials with sitagliptin had demonstrated the same differential reductions in HbA_{1c} relative to baseline, and of broadly the same extent as shown in Raz *et al*. For example:

- Nauck *et al* (2007): A 52-week trial which compared the effects of sitagliptin with a sulphonylurea (glipizide), both on a background of metformin. For both active treatments, there was a clear progression in the HbA_{1c} reduction with increasing HbA_{1c} baseline. At the highest baseline subgroup examined ($HbA_{1c} \geq 9\%$, ie slightly lower than in Raz *et al*), the reductions in the sitagliptin (n=21) and glipizide (n=33) arms were 1.68% and 1.76%, respectively.

- Aschner *et al* (2010): A 24-week study which compared sitagliptin monotherapy with metformin monotherapy. As the overall mean HbA_{1c} baseline in the study was only just over 7%, the highest baseline subgroup examined was again somewhat lower than the highest group in Raz *et al* (≥8%), but a proportionally similar result was obtained, with reductions in the sitagliptin (n=74) and metformin (n=73) arms of 1.1% and 1.2% respectively.

- Williams-Herman *et al* (2009): A 54-week trial which looked at the effects of initial therapy with sitagliptin and metformin, both separately and in combination. The highest baseline subgroup examined in this study was equivalent to that investigated in Raz *et al* (≥ 10%). The reduction in this subgroup in the sitagliptin-only arm was approximately 1.8%, and was even more marked in the patients treated with initial combination therapy (over 3% in the high-dose combination arm).

In summary Merck Sharp & Dohme submitted that the high-baseline data in the e-detail related to the primary licensed indication for the medicine. The relevant analysis was pre-specified in the study protocol and the data presented accurately reflected the findings of the study.

Every piece of information that would help a physician form an opinion as to the validity and significance of the data was included in the piece. The widely separated confidence intervals demonstrated that the numbers involved were great enough to show an effectively significant difference between the two treatment arms. Merck Sharp & Dohme submitted that the data exemplified a recognised phenomenon seen with all antidiabetic agents; and one, moreover, of great relevance to potential prescribers

The data formed part of a larger body of evidence from multiple randomised controlled trials, all of which demonstrated the same effect to proportionally the same extent.

Given the above, Merck Sharp & Dohme submitted that the information would have to be presented in a very unbalanced manner indeed to render it actively misleading.

As far as presentation was concerned, pink was not chosen for the background colour with any sinister intent; it was one of the standard Januvia livery colours and since launch had been used for a variety of design elements (headings, illustrations, backgrounds, etc). If the Panel was correct that the eye was drawn to the colour to some extent, this was surely not to the total exclusion of everything else on the page. Merck Sharp & Dohme noted that the heading and much of the text in the box showing the main trial results were also in pink. Given the natural tendency to read from left to right, the high-baseline data in the e-detail would be seen as intended: as adjunctive and supplementary information to the main results of study.

Taken in conjunction with the additional textual information supplied, Merck Sharp & Dohme submitted that a downward-pointing arrow was not an unreasonable way to represent the essentials of the data.

Merck Sharp & Dohme finally noted that when it presented the same data in the Januvia detail aid, the main results from the trial were presented in a box well over twice as wide as the circle containing the high-baseline data. While this was not possible for an electronically formatted piece, the main-results box still occupied a significantly greater area than the pink circle.

COMMENTS FROM NOVO NORDISK

Novo Nordisk fully agreed with Merck Sharp & Dohme that the relationship between baseline glycaemic control and subsequent glycaemic reduction with any antidiabetic agent was widely recognised. This was probably the reason why Raz *et al* aimed for a trial population with higher baseline HbA_{1c} than the average baseline HbA_{1c} levels in previous sitagliptin trials, as was reflected in the introduction 'Hence, the purpose of the present 30-week study was to provide additional experience with the combination therapy of sitagliptin and metformin, including experience in patients with a different range of baseline HbA_{1c} (8.0-11.0%) than was examined in these prior studies of sitagliptin as an add-on to metformin monotherapy'. Thus the trial itself with its full trial population had been designed to show a potentially larger HbA_{1c} reduction than what was observed in the previous sitagliptin trials. Therefore Novo Nordisk failed to understand Merck Sharp & Dohme's explanation that the average reductions in glycaemia reported in trials with antidiabetic agents only told part of the story of an individual agent's potential efficacy, in context with Raz *et al*. Novo Nordisk alleged that the reason to highlight the average reduction of HbA_{1c} in a small subset of patients was to overemphasise the 1.8% reduction in context with the heading of the page which promised that more patients get to goal with Janumet.

In terms of the relevance of highlighting the glycaemic results from such a subgroup, Novo Nordisk noted that the most widely recognised and followed UK clinical guideline, the NICE clinical recommendation in type 2 diabetes, suggested a general HbA_{1c} target of 6.5% with the first (OAD monotherapy) or second-line therapies (dual OAD combination). Raz *et al* reflected the latter situation (adding a second-line OAD after metformin monotherapy failure). This meant that the GP, the target audience of this promotional material, would usually consider sitagliptin as an add-on option at much lower HbA_{1c} levels than the baseline glycaemic control in the small subgroup was. Therefore, Novo Nordisk disagreed that the subgroup of patients with an average HbA_{1c} level of 10.5% would be of clinical relevance.

Novo Nordisk fully acknowledged that clinical reality could be different than the ideal treatment scenarios in the different guidelines. However even in the case of the representative UK primary care database analyses conducted and published by Calvert *et al* (2007), the average HbA_{1c} level when the second-line OAD therapy was added was 9.04% which was fairly comparable with the average baseline HbA_{1c} level of the patients in Raz *et al* (9.1%). Thus Novo Nordisk strongly believed that the emphasis on the subgroup in the material was undue, unnecessary and irrelevant from clinical perspective.

Novo Nordisk agreed with the Panel which questioned the robustness of any results from a subgroup of 19 patients even if the subgroup analysis was pre-specified in the trial protocol. Novo Nordisk clearly disagreed with Merck Sharp & Dohme's explanation that the additional 13 patients in the placebo arm would increase the robustness of the observation within the sitagliptin group. The results from a subgroup analysis could only be used

in the way Merck Sharp & Dohme used the HbA_{1c} reduction in the small subset of patients (namely placing the same emphasis on the result from the overall study cohort as on the results from the subgroup) if the robustness of such finding was substantiated by proving a statistically significant difference between the active and placebo arms with an appropriate statistical test. If no such test had been conducted (which was the case here), the difference could be merely driven by chance. Hence it was inappropriate to emphasise it in any way in a piece of promotional material unless it was clearly stated that no statistical comparison had been conducted.

On the basis of the above, Novo Nordisk upheld its position regarding the subgroup results in the material in question and agreed with the Panel's ruling of a breach of Clauses 7.2 and 7.3.

APPEAL BOARD RULING

The Appeal Board noted that the e-detail page at issue featured results taken from Raz *et al*. The authors had assumed a within-group standard deviation of 1% for measuring HbA_{1c} and that approximately 86 patients per treatment group would provide 90% power to detect a true between-group difference of 0.5% in the mean change in HbA_{1c} from baseline.

The background colour of the e-detail page at issue was mid blue and to the right of centre was a light blue box showing the placebo adjusted median change in HbA_{1c} from baseline when sitagliptin 100mg once daily was added to metformin therapy (n=95). A mid blue downward arrow showed a fall of 1% ($p<0.001$ vs placebo). To the right of the light blue box a prominent downward white arrow within a bright pink circle depicted a 1.8% placebo adjusted additional reduction in HbA_{1c} from baseline after 18 weeks in the subgroup of patients (n=19) with a baseline HbA_{1c} ≥10%.

The Appeal Board noted that both sets of data appeared prominently on the e-detail page but that only the results from the larger group had been subject to statistical analysis. Given the visual prominence of the downward white arrow, however, the Appeal Board considered that the reader would be drawn to the data from the high baseline group and would assume that it was as statistically robust as the data from the whole group, which was not so. The study was not powered to detect a difference in such a small group and in that regard the Appeal Board noted that the authors had stated that 'patients with higher baseline HbA1c also *trended* towards larger reductions in HbA_{1c}' (emphasis added).

The Appeal Board considered that the results from the high baseline HbA_{1c} group had been over emphasised and in that regard the presentation of the data in the e-detail was misleading and did not accurately reflect Raz *et al*. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was thus unsuccessful.

The Appeal Board noted Merck Sharp & Dohme's submission that the Panel's ruling of a breach of Clause 7.3 was technically in error because that clause dealt specifically with comparisons with competitor products. The Appeal Board however disagreed, Clause 7.3 dealt with comparisons generally. The Appeal Board noted that the data was derived from a parallel-group study in which sitagliptin or placebo was added to ongoing metformin therapy. The study thus compared sitagliptin/metformin combination therapy with metformin monotherapy. The Appeal Board noted its comments above and upheld the Panel's ruling of a breach of Clause 7.3. The appeal on this point was thus unsuccessful.

Complaint received **23 December 2010**

Case completed **5 April 2011**

CASE AUTH/2379/1/11

ANONYMOUS v CHIESI

Promotion of Fostair

An anonymous, non contactable complainant referred to material for Fostair (beclometasone and formoterol) on a Chiesi exhibition stand at a meeting of the British Thoracic Society (BTS). The material at issue was a copy of the journal Respiratory disease in practice which appeared to be sponsored by Chiesi and there was an advertisement for Fostair on the outside back cover. The article on the front cover of the journal was entitled 'The small airways: an important target in asthma and COPD [chronic obstructive pulmonary disease] treatment'.

The publication was of interest and relevance to the complainant's medical practice but after looking for data on the use of Fostair in COPD, given that the journal contained information about COPD and finding a web page which referred to seeking registration of Fostair for COPD, the complainant was surprised to learn that Fostair was only licensed for asthma. The complainant did not think that this important fact was clear enough on the Chiesi stand and while he would ensure that he and his colleagues had the appropriate information to inform their decisions he queried whether Chiesi's actions were appropriate.

The detailed response from Chiesi is given below.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.
The publication in question had been paid for and sponsored by Chiesi. It had been initiated as a result of a discussion between the publisher and Chiesi. The Panel noted that Respiratory disease in practice was described as an independent title supported by an unrestricted educational grant from Chiesi. This description appeared beneath the Chiesi logo.

The journal included two articles about COPD. The first was a four page article starting on the front page and was entitled 'The small airways: an important target in asthma and COPD treatment'. It mentioned the generic name of Fostair's active ingredients in relation to particle sizes and distribution in the lungs. The article referred to formulations with extrafine and ultrafine small particles that had been developed using newer hydrofluoroalkane (HFA) propellants in pressurised metered-dose inhalers pMDIs for a long acting beta$_2$-agonist (formoterol), corticosteroids (beclometasone dipropionate (BDP), ciclesonide, flunisolide) and fixed combinations (BDP/formoterol, ciclesonide/formoterol). Improved total lung deposition (TLD) had been observed with HFA inhalers compared with chlorofluorocarbon (CFC) propellant devices. The article referred to lung deposition data in asthma patients. It concluded that future studies were needed, particularly in COPD patients to determine whether improvements in distal lung deposition and small airways function with ultrafine particles were translated into clinically significant patient outcomes such as improved control of symptoms, better health-related quality of life, fewer adverse effects and reduced exacerbations.

The second article on COPD was a two page article on 'Investigation and treatment of severe chronic obstructive pulmonary disease'. The article referred to management of breathlessness and exacerbations and the National Institute for Health and Clinical Excellence (NICE) guidelines on COPD latest draft recommendations. Mention was made of inhaled steroids and long-acting beta-agonists as well as other medicines.

The editorial referred to the recently published National Clinical Strategy for COPD and that two new medicines were to be launched for COPD later in the year.

The webpage referred to by the complainant was that of a communication company which had been appointed by Chiesi to work on the prelaunch and launch of Fostair for COPD. The page included the Chiesi logo.

The advertisement for Fostair mentioned its use in asthma. It also referred to the delivery of twice as much medication to the lungs as standard metered-dose inhalers and that a third of the extrafine particles reached the small airways. It also included the claim 'For lungfuls of life'.

The publication was available from a Chiesi promotional stand at the BTS meeting. All material on the stand needed to comply with the Code. The Panel considered that the article had been used for a promotional purpose and thus its content was covered by the Code.

The question now to be addressed was whether the journal promoted Chiesi's product for an unlicensed indication. The Code stated that promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics (SPC).

The Panel noted that the articles referred to the treatment of COPD with fixed combinations of BDP and formoterol as well as the advantages for HFA propellants. The Panel considered that the distribution of the journal from Chiesi's promotional stand in effect promoted Fostair for an unlicensed indication. In addition, the Panel noted that the Fostair advertisement in the journal referred to the extrafine particles reaching the small airways. In the Panel's view this linked to the article about the treatment of COPD and references to particle size. A breach of the Code was ruled. This was misleading and did not promote rational use. Thus further breaches were also ruled.

The Authority received an anonymous complaint about material for Fostair (beclometasone and formoterol) pressurised inhalation solution on a Chiesi Limited exhibition stand. A Fostair advertisement had been published in the journal Respiratory disease in practice, Volume 21 Number 1; the article on the front cover of the journal was entitled 'The small airways: an important target in asthma and COPD [chronic obstructive pulmonary disease] treatment'. Fostair was indicated for the regular treatment of asthma where use of a combination product inhaled corticosteroid and long acting beta$_2$-agonist was appropriate. The complainant could not be contacted.

COMPLAINT

The complainant explained that at a meeting of the British Thoracic Society (BTS), copies of the issue of Respiratory disease in practice in question were available on Cheisi's stand. The publication appeared to be sponsored by Chiesi and there was an advertisement for Fostair on the outside back cover. The publication was of interest and relevance to the complainant's medical practice but after looking for data on the use of Fostair in COPD, given that the journal contained information about COPD and finding a webpage which referred to seeking registration of Fostair for COPD, the complainant was surprised to learn that Fostair was only licensed for asthma.

The complainant did not think that this important fact was clear enough on the Chiesi stand and while he would ensure that he and his colleagues had the appropriate information to inform their decisions he queried whether Chiesi's actions were appropriate.

When writing to Chiesi, the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 7.10 of the 2008 Code.

RESPONSE

Chiesi stated that Respiratory disease in practice was an independent journal title. In response to an approach from the publisher, Chiesi agreed to provide an unrestricted educational grant to fund a fixed number of issues over a set period of time. This fact was clearly declared on the front page of the journal. On page 3 of the journal, the publisher stated the following:

> 'The sponsor has no editorial input into, or control over the content of, this publication. Sponsorship is for four issues to be published in 2010. The data, opinions and statements appearing in the articles herein are those of the contributors(s) concerned; they are not necessarily endorsed by the sponsor, publisher, Editor or Editorial Board.'

The main focus of the cover article was about the role that small airways played in the pathophysiology of respiratory diseases and the various laboratory techniques used to measure small airways function. It was not concerned with the clinical management of these diseases nor their therapeutic options. When inhaled therapies were mentioned, it was with regard to their particle sizes and distributions within the lungs. The authors did not endorse or advocate any therapeutic options for any particular diseases.

Chiesi noted that the publication did not refer to Fostair by name. It was mentioned twice in the first article by the use of the generic names of its two active ingredients. In the first instance (page 3, towards the bottom), it was mentioned when the authors referred to particle sizes of inhalers. Chiesi noted that it was not mentioned in isolation but together with five other inhalers. In the second instance, (page 4, towards the top), its inhaled deposition within the lungs was mentioned. The lung deposition data quoted was from a radio-labelled imaging study. The lung deposition data was also mentioned for another inhaler in the preceding paragraph.

Chiesi submitted that neither mention of the product endorsed or advocated its use in any disease but merely stated its physical properties (particle size and its distribution pattern in the lungs after inhalation).

With regard to the advertisement for Fostair on the outside back cover, Chiesi noted that the complainant failed to mention the prescribing information which came with it. In the 'Indications' section it was clearly stated that Fostair was for use in the management of asthma. This was reinforced in two subsequent sections, 'Dosage and Administration' and 'Precautions'. The prescribing information did not state that Fostair was indicated for use in COPD. Chiesi was surprised that the complainant, who wrote as a health professional, had not read the prescribing information before submitting the complaint.

Chiesi denied any breach of the Code.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. 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 were judged on the evidence provided by the parties.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The publication in question had been paid for and sponsored by Chiesi. It had been initiated as a result of a discussion between the publisher and Chiesi. The Panel noted that Respiratory disease in practice was described as an independent title supported by an unrestricted educational grant from Chiesi. This description appeared beneath the Chiesi logo.

The journal included two articles about COPD. The first was a four page article starting on the front page and was entitled 'The small airways: an important target in asthma and COPD treatment'. It mentioned the generic name of Fostair's active ingredients in relation to particle sizes and distribution in the lungs. The article referred to formulations with extrafine and ultrafine small particles that had been developed using newer hydrofluoroalkane (HFA) propellants in pressurised metered-dose inhalers pMDIs for a long acting beta2-agonist (formoterol), corticosteroids (beclometasone dipropionate (BDP), ciclesonide, flunisolide) and fixed combinations (BDP/formoterol, ciclesonide/formoterol). Improved total lung deposition (TLD) had been observed with HFA inhalers compared with chlorofluorocarbon (CFC) propellant devices. The article referred to lung deposition data in asthma patients. It concluded that future studies were needed, particularly in COPD patients to determine whether improvements in distal lung deposition and small airways function with ultrafine particles were translated into clinically significant patient outcomes such as improved control of symptoms, better health-related quality of life, fewer adverse effects and reduced exacerbations.

The second article on COPD was a two page article on 'Investigation and treatment of severe chronic obstructive pulmonary disease'. The article referred to management of breathlessness and exacerbations and the National Institute for Health and Clinical Excellence (NICE) guidelines on COPD latest draft recommendations. Mention was made of inhaled steroids and long-acting beta-agonists as well as other medicines.

The editorial referred to the recently published National Clinical Strategy for COPD and that two new medicines were to be launched for COPD later in the year.

The webpage referred to by the complainant was that of a communication company which had been appointed by Chiesi to work on the prelaunch and launch of Fostair for COPD. The page included the Chiesi logo.

The advertisement for Fostair mentioned its use in asthma. It also referred to the delivery of twice as much medication to the lungs as standard metered-dose inhalers and that a third of the extrafine particles reached the small airways. It also included the claim 'For lungfuls of life'.

The publication was available from a Chiesi promotional stand at the BTS meeting. All material on the stand needed to comply with the Code. The Panel considered that the article had been used for a promotional purpose and thus its content was covered by the Code.

The question now to be addressed was whether the journal promoted Chiesi's product for an unlicensed indication. Clause 3.2 stated that promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics (SPC).

The Panel noted that the articles referred to the treatment of COPD with fixed combinations of BDP and formoterol as well as the advantages for HFA propellants. The Panel considered that the distribution of the journal from Chiesi's promotional stand in effect promoted Fostair for an unlicensed indication. In addition, the Panel noted that the Fostair advertisement in the journal referred to the extrafine particles reaching the small airways. In the Panel's view this linked to the article about the treatment of COPD and references to particle size. A breach of Clause 3.2 was ruled. This was misleading and did not promote rational use. Thus breaches of Clauses 7.2 and 7.10 were also ruled.

Complaint received **4 January 2011**

Case completed **1 April 2011**

CASE AUTH/2383/2/11

ANONYMOUS GENERAL PRACTITIONER v BAYER

Yasmin journal advertisement

An anonymous and non-contactable general practitioner alleged that a journal advertisement for the oral contraceptive Yasmin (ethinylestradiol and drospirenone) issued by Bayer Healthcare, was misleading and could put patients at unnecessary risk.

A bullet point stated that Yasmin had been shown to have a beneficial effect vs baseline on acne, fluid retention, hirsutism and premenstrual symptoms. The complainant was concerned that the advertisement read as if it were asking him to prescribe Yasmin in these conditions and noted that at least three of them were listed as adverse events in the Yasmin summary of product characteristics (SPC).

The detailed submission from Bayer is given below.

The Panel noted that the 'headline' claim 'Yasmin. It's for more women than you might imagine' was immediately followed by claims in much smaller type, the first two of which were that Yasmin was an effective and well-tolerated contraceptive and that 95% of users reported overall satisfaction. The claim at issue followed: 'Yasmin has also been shown to have a beneficial effect vs baseline on acne[5]*, fluid retention[6]*, hirsutism[7]* and premenstrual symptoms[8]*'. This was followed by the claim 'Yasmin is licensed for oral contraception' beneath which, in a smaller type size again, was the explanation '*Acne and fluid retention may be uncommon side effects of COC [combined oral contraceptive] use. Yasmin is not licensed as a treatment for acne, hirsutism, fluid retention or premenstrual symptoms. ^A non-comparative study'. The product logo to the right of the claim at issue included the strapline 'Contraception and more'.

The Panel noted that there was a difference between promoting a medicine for its licensed indication and promoting additional clinical benefits. Whilst the Panel considered that it was not unacceptable to refer to a medicine's additional clinical benefits, such benefits must be referred to within the context of the licensed indication and not presented such as to imply that they were the reason, *per se*, to prescribe. Statements to the contrary were unlikely to negate an otherwise misleading impression. The Panel considered that overall the claim that Yasmin was 'for more women than you might imagine' and the strapline 'Contraception and more' would encourage readers to consider prescribing Yasmin for more than just its oral contraceptive efficacy ie its positive effects on acne, fluid retention, hirsutism and premenstrual symptoms.

The acne claim was referenced to a study which demonstrated the non inferiority of Yasmin compared with Dianette (which was licensed for severe acne refractory to prolonged oral antibiotic therapy). The fluid retention claim was referenced to a non comparative prospective study which showed an improvement in abdominal bloating and breast tenderness. The claim for a beneficial effect on premenstrual symptoms was referenced to an in-house literature search in which thirteen studies were identified, five of which included an active or placebo comparator. All showed a positive trend on one or more premenstrual symptoms with Yasmin. Many showed statistically significant results. Conversely, the Panel noted that depressive mood, changes in libido and fluid retention were listed on the SPC as possible adverse reactions.

The Panel noted that the advertisement stated that 'acne and fluid retention *may* be uncommon side effects of COC use' (emphasis added). The Yasmin SPC stated that both effects had been reported during use with Yasmin. The Panel considered that the advertisement underplayed the side-effects of Yasmin. A breach of the Code was ruled.

The Panel noted Bayer's submission regarding the adverse reactions in the SPC and that these included treatment emergent adverse events irrespective of whether they were thought to be caused by the medicine. The Panel considered that the advertisement promoted clinical effects of Yasmin which were not licensed indications and the converse of which were listed as adverse reactions in the SPC. In the Panel's view the advertisement encouraged prescribers to consider these features as a reason to prescribe Yasmin. Further, some of the data referred to in the advertisement was non comparative. The Panel considered that overall the advertisement was misleading and inconsistent with the SPC. Breaches of the Code were ruled.

The Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected but considered that to imply possible clinical uses that were not licensed, such that a counter claim was considered necessary, was a serious matter. Further, citing possible clinical advantages the opposite of which were listed in the SPC as potential side effects was of serious concern. The Panel did not consider that the statement 'Acne and fluid retention may be uncommon side effects of COC use' negated the impression otherwise given. A breach of Clause 2 was ruled.

An anonymous and non-contactable general practitioner complained about an advertisement (ref UK.PH.WH.YSM.2010.119) for Yasmin

(ethinylestradiol and drospirenone) published in Pulse, 26 January 2011, by Bayer Healthcare. Yasmin was indicated for oral contraception.

COMPLAINT

The complainant stated that he regularly prescribed Yasmin for his patients.

The third bullet point in the advertisement stated that Yasmin had also been shown to have a beneficial effect vs baseline on acne, fluid retention, hirsutism and premenstrual symptoms.

The complainant was concerned firstly that the advertisement read as if it were asking him to prescribe Yasmin in the above mentioned conditions, and secondly that at least three of these were recognised adverse events of Yasmin and listed in the current summary of product characteristics (SPC).

The complainant believed it was highly unethical to put such misleading information into an advertisement and that it could put patients at unnecessary risk.

When writing to Bayer, the Authority asked it to respond in relation to Clauses 2, 3.2, 7.2 and 7.9 of the Code.

RESPONSE

Bayer noted that the advertisement read as follows:

- 'Yasmin is an effective and well-tolerated contraceptive
- 95% of users report overall satisfaction with Yasmin, the most widely used pill in Europe
- Yasmin has also been shown to have a beneficial effect vs baseline on acne, fluid retention, hirsutism and premenstrual symptoms
  Yasmin is licensed for oral contraception'.

Bayer submitted that it was clear, upfront, from the advertisement that Yasmin was a contraceptive. Moreover, the licensed indication was re-stated in the main bulk of the copy. The advertisement did not suggest that Yasmin was licensed for acne, fluid retention, hirsutism or premenstrual symptoms, and in fact this was explicitly stated in the adjacent text with the words 'Yasmin is not licensed as a treatment for acne, hirsutism, fluid retention or premenstrual symptoms'.

The language used in the advertisement was factual. It was intended to alert a potential prescriber to the properties of Yasmin with regard to these common co-morbid conditions, which was important when making a prescribing decision because combined oral contraceptives (COCs) could worsen some of these conditions. Yasmin had a positive effect on the listed conditions as a result of its antiandrogenic and mild antimineralocorticoid properties, which were described in Section 5.1 of the SPC. Clinical studies substantiating the beneficial effects were discussed below.
In addition, in 2009 the Medicines and Healthcare products Regulatory Agency (MHRA) reviewed the claim 'Drospirenone has a positive effect on acne and fluid retention' particularly with regard to whether the claim about fluid retention could be substantiated. Although the complaint was upheld, importantly, the MHRA allowed the claim regarding fluid retention to be made as long as a previously agreed claim from pre-vetting was used in future advertisements. Bayer had adhered to this.

In summary, Bayer believed its advertisement was consistent with the SPC and it therefore denied a breach of Clause 3.2.

Bayer noted that Yasmin had been on the UK market for 9 years and there was now a substantial body of evidence to support the beneficial effects on acne, fluid retention, hirsutism and premenstrual symptoms. The beneficial effects on acne were largely related to the antiandrogenic properties of drospirenone which were discussed further in the SPC. In the advertisement, the claim with regard to acne was referenced to a double blind study comparing Yasmin with Dianette (ethinylestradiol and cyproterone acetate) over 9 treatment cycles (van Vloten et al, 2002). One hundred and twenty-eight women with mild-to-moderate facial acne were randomized to receive either Yasmin or Dianette in a 2:1 ratio. The results showed that, from baseline, the reduction in acne lesions was 62.5% and 58.8% respectively for Yasmin and Dianette.

Statistical analysis demonstrated non-inferiority for Yasmin vs Dianette ($p=0.0006$) which indicated that Yasmin was at least as effective as Dianette in improving the acne lesion count at the end of 9 treatment cycles. The authors concluded that Yasmin was as effective for treating mild-to-moderate acne as Dianette. This was clinically relevant because Dianette was licensed for severe acne refractory to prolonged oral antibiotic therapy.

Bayer noted that a similar claim, 'A demonstrable positive effect on … skin condition', was considered in Case AUTH/1352/8/02; the Panel ruled no breach.

Yasmin's positive effects on fluid retention were largely related to the mild antimineralocorticoid effects of drospirenone, which were discussed further in the SPC and could be substantiated by Apter *et al*, (2003) and Endrikat *et al*, (2009).

Apter *et al* (reference number 6 in the advertisement), was a single-arm prospective study. General well-being and fluid-related symptoms were measured at baseline and again after 6 cycles of Yasmin. 177 women (77.3%) showed improvement in the severity of abdominal bloating during the luteal phase ($p<0.001$); 158 (69%) showed improvement in the severity of breast tension ($p<0.001$) and 119 (52% showed improvement in the severity of swelling of the extremities (p=ns). This study clearly demonstrated an improvement

between baseline and cycle 6 of treatment in two major somatic symptoms associated with fluid retention, with a non-significant positive trend in swelling of extremities. In keeping with what was agreed with the MHRA in 2009, the nature of this trial was clearly identified through the words 'a non-comparative study' in the advertisement.

Endrikat *et al* (part of reference number 8 in the advertisement) was a single-arm prospective study of 3,488 women. Outcomes including premenstrual symptoms of water retention were measured at baseline and after three and six cycles of Yasmin. The results, clearly demonstrated a statistically significant improvement in all fluid-related parameters vs baseline.

Reference number 8 'data on file' in the advertisement referred to the results of an in-house literature search to evaluate the body of evidence for the effects of Yasmin on fluid retention and premenstrual symptoms. There were many studies of differing designs. Many showed statistically significant results supporting the effect of Yasmin; the remainder generally showed positive trends. Therefore Bayer believed that Apter *et al* and Endrikat *et al* reflected the overall substantial existing body of evidence.

Bayer noted that premenstrual symptoms was the name given to the physical, psychological and behavioural symptoms that could occur in the two weeks before menstruation. Definition of premenstrual symptoms typically included breast tenderness, mood swings, irritability, loss of interest in sex and fluid retention'. Yasmin's positive effect on premenstrual symptoms was largely related to the mild antiandrogenic and antimineralocorticoid effects of drospirenone, which were discussed further in the SPC.

The beneficial effect of Yasmin on premenstrual symptoms was referenced in the advertisement to 'data on file'. This referred to the in-house literature search to evaluate the body of evidence for the effects of Yasmin on fluid retention and on premenstrual symptoms. Thirteen papers were identified, five of which were studies with an active or placebo comparator. All studies showed a positive trend on one or more symptoms with Yasmin.

Yasmin had also been recommended in several recognised clinical guidelines for the management of premenstrual symptoms and fluid retention, most notably in the National Association for Premenstrual Syndrome (NAPS) premenstrual symptoms treatment guideline.

Many of the studies referred to above showed statistically significant results supporting the effect of Yasmin. The principal ones were as follows:

- Guang-Sheng *et al* (2010), a randomised, open-label, multicentre study in 768 women, compared Yasmin with Marvelon (30mcg ethinylestradiol and 150mcg desogestrel), randomized 3:1. As part of the secondary endpoint, as well as a global assessment, the Menstrual Distress Questionnaire (MDQ) was administered at baseline, visit 3 (cycle 7) and visit 5 (after cycle 13). According to the MDQ subscale, water retention during the inter-menstrual period, and water retention and general well-being during the menstrual period in the Yasmin group (-0.297, -0.057, 0.033 and 0.150, respectively), were significantly improved compared with the Marvelon group (-0.108, 0.023, 0.231 and -0.023, respectively) [all $p<0.05$]. The authors concluded that Yasmin had a more favourable effect on premenstrual symptoms than Marvelon.

- Kelly *et al* (2010), a randomized, single blind, parallel-group, multicentre study in 280 women, compared Yasmin with Microgynon (30mcg ethinylestradiol and 150mcg levonorgestrel). The primary outcome measured was the change in the overall score for the MDQ from randomization to cycle 6. Secondary outcomes of menstrual symptoms, and subjective well-being were also measured. Treatment with Yasmin and Microgynon had similar beneficial effects on symptoms of fluid retention and impaired concentration. However Yasmin was significantly better in alleviating negative affect symptoms during the menstrual phase (median difference in MDQ T score -3; $p=0.027$). More subjects in the Yasmin group reported improved physical well-being (60% vs 46%; $p=0.035$).

- Sangthawan and Taneepanichskul (2005), a randomized, open-label study in 99 women, compared Yasmin with Microgynon. The primary outcome measured the prevalence of premenstrual symptoms at cycle 6, while the secondary outcome measured changes from baseline in the Women's Health Assessment Questionnaire (WHAQ) categories (a subset of items from the MDQ). At cycle 6, the prevalence of premenstrual symptoms in the Yasmin group was significantly lower than that of the Microgynon group (32% vs 61.2%; $p=0.005$). In the premenstrual phase, the Yasmin group showed a greater improvement of mean scores from baseline vs Microgynon on negative affect as seen in the items on anxiety, irritability, feeling sad or blue and weight gain in the category of water retention.

- Freeman *et al* (2001), a randomized, double-blind, multicentre, placebo-controlled study in 82 women, evaluated the efficacy of Yasmin in the treatment of premenstrual dysphoric disorder (PMDD), which was a severe form of premenstrual symptom, over 3 treatment cycles. The primary endpoint measured changes from baseline in scores on the Calendar of Premenstrual Experiences (COPE) scale. The study revealed greater improvement in the total COPE scores in the Yasmin group compared with the placebo group. The results of this study showed a consistent trend in reduction of

symptoms that suggested a beneficial effect of Yasmin for the treatment of PMDD, despite limitations of the study design.

- Apter *et al* showed a significant increase in overall Psychological General Well-Being Index (PGWBI) scores from baseline of 16.9 and 20.8 points at cycles 3 and 6, respectively ($p<0.0001$) in women suffering from PMS, demonstrating an improvement in psychological general well-being with treatment.

- Endrikat *et al* showed a statistically significant improvement in all of the satisfaction parameters measured:

Question	Strength of positive trend vs baseline
Are you satisfied with your body weight?	p<0.0001
How do you feel before menses?	p<0.0001
Your skin is…	p<0.0001
Do you have mood swings?	p<0.0001
Do you feel depressed?	p<0.0001
Do you have trouble sleeping?	p<0.0001
Do your breasts feel tender or uncomfortable?	p<0.0001
Do you feel physically attractive?	p<0.0001
Overall quality of life during the last month	p<0.0001

The remainder of the studies identified in Bayer's literature search showed either statistically significant results for improvements in premenstrual symptoms or positive trends. Consequently the body of evidence supported Bayer's statement that Yasmin had a beneficial effect vs baseline on premenstrual symptoms.

Bayer noted that a similar claim, 'demonstrable positive effect on PM (premenstrual) symptoms', had been at issue in Case AUTH/1352/8/02. The differences from the present case were that:

- Since the PMCPA's ruling in 2002 more studies had been published and there was now further substantial evidence to support the clinical effect of Yasmin in fluid retention and premenstrual symptoms.

- Since the 2002 PMCPA ruling, Yasmin had also been recommended in several recognised clinical guidelines for the management of premenstrual symptoms and fluid retention, most notably in the NAPS treatment guideline and suggested in a leading textbook for clinicians 'Contraception: Your Questions Answered'(Guillebaud).

Bayer noted that Yasmin's positive effects on hirsutism were, like acne, largely related to the antiandrogenic effects of drospirenone, which were discussed further in the SPC. In the advertisement the claim with regard to hirsutism was referenced to Batukan *et al*, (2007), a double blind study which compared Yasmin with Dianette over 12 months. Ninety-one women with moderate-to-severe hirsutism were randomized to receive either Yasmin or Dianette, which was licensed for moderately severe hirsutism. The results showed that the median reduction of total hirsutism score from baseline was 80% and 81% respectively for Yasmin and Dianette. The authors concluded that both treatments had a similar effect on reducing body hair growth.

The effect of Yasmin on hirsutism, specifically hair growth on the upper lip and chin, was also measured as a secondary outcome in van Vloten *et al*. During treatment hair growth decreased in both the Yasmin and Dianette treatment groups and completely resolved in most cases. By cycle 9, the percentage of subjects without upper lip hair had increased from 65.5% to 84.5% and 66.7% to 87.9% in the Yasmin and Dianette groups respectively. Similarly, the percentage of subjects without chin hair increased from 84.5% to 93.1% and 90.9% to 97.0% in the Yasmin and Dianette groups respectively.

In summary, Bayer submitted that the claims in the advertisement about Yasmin's non-contraceptive properties could be substantiated and were a fair reflection of the overall body of evidence supporting the beneficial effects of Yasmin. Bayer denied a breach of Clause 7.2.

With regard to adverse events, Bayer recognised that acne and fluid retention were listed in the current SPC as uncommon side effects. Given that this was explicitly stated in the advertisement Bayer considered that there was no danger that a prescriber would be misled.

Moreover, Bayer did not consider that the description of the non-contraceptive properties of Yasmin in the advertisement was incompatible with these being stated as possible uncommon side effects of Yasmin use. This was due to two key factors, namely the methodology of collecting and interpreting safety data for inclusion in the SPC; and secondly the 2009 correspondence with the MHRA about fluid retention.

Historically, inclusion of undesirable effects in Section 4.8 of the SPC was dependent on the frequency of adverse drug reactions (in which a causal relationship between the medicine and an adverse reaction was suspected). This was the methodology used for most other COCs currently on the UK market, most of which were licensed in the 1970s or early 80s. However, current methodology included all treatment emergent adverse events occurring at a particular frequency, irrespective of whether they were thought to be caused by the medicine. Adverse events were defined as any untoward event, regardless of whether it was thought to be causally related to the medicine. The Yasmin SPC was based on this modern methodology.

The listing of adverse events as opposed to just adverse reactions was considered safer, for

example because sometimes a previously unknown causal relationship could emerge only in hindsight. However, the downside was a potential listing of unrelated 'side effects', because although a condition might arise during treatment, this did not necessarily imply a causal relationship with the medicine; it might just be a common co-morbid condition that existed in the population receiving the medicine.

Moreover, despite the fact that fluid retention was listed as an uncommon side effect in the Yasmin SPC, in 2009 the MHRA accepted that the claim regarding a beneficial effect on fluid retention could still be used, as long as it was made clear that this could also be an uncommon side effect. Bayer had complied with this request. Therefore, there was no incompatibility with a non-contraceptive beneficial property also being listed as a side effect.

Therefore, Bayer did not consider the reference to the beneficial non-contraceptive properties of Yasmin was misleading or in breach of Clause 7.9.

In summary, Bayer did not consider the description of the additional non-contraceptive properties of Yasmin was misleading or unethical. Most importantly, Bayer strongly maintained that it had not put patients at risk. Bayer considered that it had acted in a highly ethical, balanced and transparent manner and it denied breaches of Clauses 2, 3.2, 7.2 or 7.9.

PANEL RULING

The Panel noted that the 'headline' claim in the advertisement was 'Yasmin. It's for more women than you might imagine'. This was immediately followed by claims in much smaller type, the first two of which were that Yasmin was an effective and well-tolerated contraceptive and that 95% of users reported overall satisfaction. The claim at issue followed: 'Yasmin has also been shown to have a beneficial effect vs baseline on acne5*, fluid retention6*, hirsutism7* and premenstrual symptoms8*'. This was followed by the claim 'Yasmin is licensed for oral contraception' beneath which, in a smaller type size again, was the explanation '*Acne and fluid retention may be uncommon side effects of COC use. Yasmin is not licensed as a treatment for acne, hirsutism, fluid retention or premenstrual symptoms. ^A non-comparative study'. The product logo to the right of the claim at issue included the strapline 'Contraception and more'.

The Panel noted that there was a difference between promoting a medicine for its licensed indication and promoting its additional clinical benefits. Whilst the Panel considered that it was not unacceptable to refer to a medicine's additional clinical benefits, such benefits must be referred to within the context of the licensed indication and not presented such as to imply that they were the reason, *per se*, to prescribe. Statements to the contrary were unlikely to negate an otherwise misleading impression. The Panel considered that overall the claim that Yasmin was 'for more women than you might imagine' and the strapline 'Contraception and more' would encourage readers to consider prescribing Yasmin for more than just its oral contraceptive efficacy ie its positive effects on acne, fluid retention, hirsutism and premenstrual symptoms.

The SPC stated in Section 4.8, Undesirable effects, that fluid retention and acne were uncommon adverse reactions (<1 in 100, ≥1 in 1000). Section 5.1 of the SPC, Pharmacodynamic properties, stated that in a therapeutic dosage, drospirenone possessed antiandrogenic and mild antimineralocorticoid properties and had a pharmacological profile closely resembling the natural hormone progesterone. This section also stated that there were indications from clinical studies that the mild antimineralocorticoid properties of Yasmin resulted in a mild antimineralocorticoid effect. There was no similar statement regarding the antiandrogenic properties of drospirenone and no reference in the SPC specifically about positive effects on acne, fluid retention, hirsutism or premenstrual symptoms.

The Panel noted that Clause 3.2 required the promotion of a medicine to be in accordance with the terms of its marketing authorization and not inconsistent with the particulars listed in the SPC.

The acne claim was referenced to van Vloten *et al* which demonstrated the non inferiority of Yasmin compared with Dianette (which was licensed for severe acne refractory to prolonged oral antibiotic therapy). The fluid retention claim was referenced to Apter *et al*, a non comparative prospective study which showed an improvement in abdominal bloating and breast tenderness. Endrikat *et al*, a single arm prospective study showed a statistically significant improvement in all fluid-related parameters (abdominal bloating, breast tenderness and swollen extremities) vs baseline. Thirteen studies were identified, five of which included an active or placebo comparator. All showed a positive trend on one or more premenstrual symptoms with Yasmin. Many showed statistically significant results.

The claim for a beneficial effect on premenstrual symptoms was based on a literature search by Bayer to evaluate all the evidence for the positive effects of Yasmin on breast tenderness, mood swings, irritability, loss of interest in sex and fluid retention. Conversely, depressive mood, changes in libido and fluid retention were listed on the SPC as possible adverse reactions.

The Panel noted that the advertisement stated that 'acne and fluid retention *may* be uncommon side effects of COC use' (emphasis added). The Yasmin SPC stated that both effects had been reported during use with Yasmin. The Panel considered that the advertisement underplayed the side-effects of Yasmin. A breach of Clause 7.9 was ruled.

The Panel noted Bayer's submission regarding the

adverse reactions in the SPC and that these included treatment emergent adverse events irrespective of whether they were thought to be caused by the medicine. The Panel considered that the advertisement promoted clinical effects of Yasmin which were not licensed indications and the converse of which were listed as adverse reactions in the SPC. In the Panel's view the advertisement encouraged prescribers to consider these features as a reason to prescribe Yasmin. Further, some of the data referred to in the advertisement was non comparative. The Panel considered that overall the advertisement was misleading and inconsistent with the SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

With regard to Clause 2, the Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected but considered that to imply possible clinical uses that were not licensed, such that a counter claim was considered necessary, was a serious matter. Further, citing possible clinical advantages the opposite of which were listed in the SPC as potential side effects was of serious concern. The Panel did not consider that the statement 'Acne and fluid retention may be uncommon side effects of COC use' negated the impression otherwise given. A breach of Clause 2 was ruled.

Complaint received **7 February 2011**

Case completed **24 March 2011**

ANONYMOUS v BAYER

Meeting arrangements and conduct of a representative

An anonymous general practitioner complained about the arrangements for a meeting and the conduct of a representative from Bayer Healthcare.

The complainant stated that in September 2010 she paid to attend a family planning update organised by a commercial events company linked to a university.

It was clear that Bayer had a very big influence on the content of the meeting even though this was not advertised. It was like sitting through presentations written by Bayer; they were promotional and placed Bayer's products in almost all scenarios by the presenters. This was not what the complainant had paid for.

Following the meeting the complainant alleged that she was forced to speak with the representative in question who was very aggressive in telling the complainant about how Bayer's products would suit the complainant's patients! The representative was desperate to make sure that the complainant agreed with what she said before the complainant was allowed to leave. The complainant felt undermined, compromised and very intimidated by the representative, in fact she felt bullied. The complainant stated that a few of the other delegates had told her that the representative had approached them in the same way.

There was talk of the commercial events company being an un-disclosed front for Bayer as all of the events it arranged were sponsored by the representative.

The Panel noted that the meeting was arranged by a commercial events company which invited Bayer and one other company to sponsor it. Bayer stated that it had no relationship with the events company other than to provide sponsorship for medical education events. According to Bayer it had no influence over the selection of speakers or the content of the meeting. Neither Bayer nor its representatives had invited delegates and it had neither briefed nor entered into a contract with the speaker. The sponsorship invoice referred to meeting costs, speaker fees, room hire and refreshments.

The half day meeting was entitled 'Current Challenges in General Practice' and the agenda referred to two presentations: the first entitled 'IUD/IUS Update Workshop: Putting Contraception into Practice'. The second presentation was in a different therapy area. The front page of the invitation referred to Bayer's sponsorship. The presentation delivered was entitled 'Intrauterine methods open Surgery' and presented seven patient scenarios and discussed treatment options:

The first scenario advised that the National Institute for health and Clinical Excellence (NICE) guidance on long-acting reversible contraceptives identified copper devices containing 380mm^2 copper as 'the most effective.' Two devices, Tsafe 380A and Bayer's device TT380 slimline were described as 'WHO gold standard'. A photograph of each device was followed by a slide headed 'Cumulative pregnancy rates' which featured data for a range of devices and Mirena (levonorgestrel+IUD) which was a Bayer product. Subsequent scenarios referred to intrauterine devices produced by other manufacturers. Contrary to Bayer's submission its products were mentioned by brand name.

There was no evidence before the Panel that the commercial events company was acting as Bayer's agent. Nonetheless the Panel did not consider that the arrangements for the meeting were at arm's length as described by Bayer. The Panel noted that the meeting was organised by a commercial events company, featured a presentation in an area of commercial interest for Bayer, was attended by two of its representatives and was partly sponsored by Bayer as set out in the invoice. In such circumstances the Panel considered that it was beholden upon Bayer to ensure that it was an appropriate meeting to sponsor and at the very least that the overall arrangements did not circumvent the requirements of the Code.

The Panel noted its comments about Bayer's role and responsibility in relation to the meeting as described above. The Panel noted that the front page of the invitation was headed at the top with the name of the events company and stated at the bottom of the page that the meeting was sponsored by Bayer Schering Pharma. The Panel considered that the design of the invitation and the declaration of sponsorship was such that Bayer's role was sufficiently clear. No breach of the Code was ruled.

Whilst the presentation did mention Bayer's products such references appeared relevant to the scenarios described and the Panel did not consider that there was a disproportionate emphasis on them as alleged. Other products were referred to. In addition the Panel noted that the Code applied, *inter alia*, to the promotion of medicines to health

professionals and appropriate administrative staff. Medicines were defined in the Code as any branded or unbranded medicine intended for use in humans which requires a marketing authorization. The Code did not apply to the promotion of devices, save where the devices could only be used with a specific medicine. One slide, however, referred to Mirena which was a licensed medicine. Bayer had not submitted that the Code did not apply to the presentation. Irrespective of whether Bayer was responsible for the content of the presentation and taking all the circumstances into account the Panel did not consider that the presentation constituted disguised promotional material and no breach of the Code was ruled. Noting its rulings above the Panel did not consider that the company had failed to maintain high standards and ruled no breach of the Code.

The complainant alleged that, following the meeting whilst in conversation with the representative, she had felt undermined, compromised and very intimidated. Bayer, however, submitted that the representative identified by the complainant had spoken to just two delegates before the meeting started and had left by the end of the meeting. The second representative, had remained at the exhibition stand throughout the meeting and thus had only spoken to delegates who proactively approached him. According to Bayer he did not notice a negative reaction from any delegate following their interaction with him.

The Panel noted that great dissatisfaction was usually necessary on the part of a health professional before he/she was moved to submit a complaint. Nonetheless in such circumstances it was impossible to determine where on the balance of probabilities the truth lay. The Panel thus ruled no breach of the Code including no breach of Clause 2.

An anonymous and non-contactable general practitioner complained about the arrangements for a meeting and the conduct of a representative from Bayer Healthcare.

COMPLAINT

The complainant stated that in September 2010 she paid to attend a family planning update organised by a commercial events company which was linked to a university. The complainant attended so that she could keep up to date with changes in family planning which was becoming more important in her practice and as the only female partner she saw most of the patients regarding this.

At the meeting it was clear that Bayer had a very big influence on the content of the meeting even though this was not advertised. During the seminar it was like sitting through presentations written by Bayer; they were promotional and placed Bayer's products in almost all scenarios by the presenters. This was not what the complainant had paid for.

Following the meeting the complainant was forced to speak with the representative in question who had organised the meeting and she was very aggressive in telling the complainant about how Bayer's products would suit the complainant's patients! Again the complainant had not paid to attend this meeting to be sold to like a timeshare tout did to a holiday maker. The complainant was a captive audience and the representative was desperate to make sure that the complainant agreed with what she said before the complainant was allowed to leave. The complainant felt undermined, compromised and very intimidated by the representative, in fact she felt bullied.

The complainant stated that a few of the other delegates had told her that the representative had approached them in the same way and that she worked with a primary care trust (PCT). The complainant queried whether the representative had influenced them in a similar manner too. This was completely wrong. A representative should only provide information about their company's product to let doctors decide if those products were suitable to use for the patient and should not pressurise doctors into thinking otherwise.

There was talk of the commercial events company being an un-disclosed front for Bayer as all of the events it arranged were sponsored by the representative; perhaps she was profiting from them? The complainant thought this should be investigated.

The complainant would not attend any more training organised by the commercial events company and would not attend any organised by the university if they were supported by Bayer. She would travel outside of the area to avoid the hard sell she had had to endure; she had stopped seeing representatives from all companies following this incident.

When writing to Bayer, the Authority asked it to respond in relation to Clauses 2, 9.1, 12.1, 15.2 and 19.3 of the 2008 Code.

RESPONSE

Bayer stated that as the complainant had not given a specific date or venue it assumed that the meeting at issue was one that was held on 30 September, 2010. This meeting was attended by two of Bayer's representatives, one of which was the representative named by the complainant. The named representative had been interviewed by the national sales director, to gain an account of the meeting and to allow her to reply to the complainant's specific allegations. The representative refuted all claims made by the complainant.

Bayer stated that its relationship with the events company was one of sponsor only. Bayer was one of four companies which had agreed to sponsor eight meetings in 2010. The meeting was sponsored by Bayer and a devices company. The invoice issued by the events company showed that this sponsorship was used toward meeting costs, speaker fees, room hire and refreshments. Other than the provision of sponsorship for medical education events, Bayer did not have any business connection with the events company, and the complainant's suggestion that the events company was a 'front' for Bayer was completely misplaced. Likewise the representative in question had no personal connection with the events company and strongly refuted the allegation that she obtained a financial benefit, either directly or indirectly, from Bayer's sponsorship of the company.

The meeting was arranged and organised by the events company. Bayer and a devices company were only involved as financial co-sponsors of the meeting at the request of the events company; neither company had any direct involvement in the organisation of the event and in particular they had no influence over the selection of the speakers or the content of the meeting. As such Bayer had no reason to brief or enter into a contract with the speaker involved in this event. The company's sponsorship was clearly stated on the invitation and the agenda. Bayer noted that no delegate was asked to pay to attend this meeting. The £10 deposit requested by the events company was refunded to every delegate who attended on the day.

Bayer provided a copy of the invitation. As meetings approval was done electronically, the e-mail trail which demonstrated business manager approval of this meeting in line with Bayer's standard operating procedure (SOP) was provided as was the SOP-101 and the associated meeting authorization form. No follow up materials were issued after the meeting and therefore no approvals were required.

Bayer also provided a copy of the events company agenda. As this was an arm's length arrangement Bayer did not need to approve the speaker slides. However Bayer had obtained a copy of the slide set used by the speaker, an associate specialist from a local community sexual health team. As could be seen from the invitation and agenda the other topic was nicotine replacement; Bayer did not have a copy of those slides.

Bayer submitted that no materials were prepared for representatives and as such no approvals were carried out.

The meeting was attended by eighteen nurses and doctors. In terms of the tone of the meeting, the consolidated feedback supplied by the events company showed that the average score was 4.8/5 for the session which Bayer assumed the complainant had referred to. Bayer believed, contrary to the complainant's view, that this suggested a very high degree of satisfaction from the delegates. If an individual was emotionally affected as suggested in the complaint this might have been a very good opportunity to make that known anonymously via the feedback questionnaire.

Having looked at the speaker's slides Bayer believed that they covered the whole range of long-acting reversible contraception methods as well as emergency contraception and oral contraception in a balanced way and did not mention Bayer's products by brand name, despite most of its competitors being mentioned by brand name.

Bayer stated that the representative was understandably deeply hurt by the complainant's comments that she'd been spoken to 'in an aggressive manner akin to a timeshare tout' and considered her professionalism had been questioned. The representative was at the meeting to ensure that the Bayer stand was set up in the correct place and that everything was there that was needed. The representative had spoken with only two delegates before the meeting started and on neither occasion did she consider she was aggressive or rude. One delegate was a GP that the representative knew and they discussed the recent death of the customer's father; the other delegate said 'Hello' to the representative and moved on to talk with her colleague without further conversation. The complainant mentioned that she was 'forced to speak with the representative after the meeting'. The representative had left the meeting by then so it was difficult to see how the complainant or indeed any other delegate could have been forced to speak with her.

Bayer had never doubted the representative's professionalism or integrity. She was a valued and highly competent member of Bayer's field based team and as such it was very surprised to see these allegations made against her.

The representative was employed as a healthcare development manager and as such a large part of her role required her to work with members of a PCT's management team such as pharmaceutical advisors and medicine management personnel. Bayer was therefore not surprised to hear that the representative worked with the local PCT. Like all Bayer's HDMs the representative worked within the Code and was updated to ensure compliance.

In summary, Bayer did not consider there were grounds to uphold the complaint. It denied the implication that the meeting or the representative's conduct failed to maintain the 'high standards' required by Clauses 9.1 and 15.2. Bayer also refuted that the meeting was disguised promotion (Clause 12.1). This was evidenced by the invitation, agenda and delegate feedback where both the subject matter and Bayer's sponsorship were clear and prominent (Clause 19.3). Therefore it followed

that Bayer also did not consider there to be any justification to support a breach of Clause 2.

In response to a request for further information Bayer confirmed the identity of the second representative attending the meeting and that he was present at the conclusion of the meeting and did speak with a number of delegates.

Bayer confirmed that the second representative spoke with a number of delegates throughout the course of the meeting and discussed the company's promoted brands in line with the Code. He remained at the Bayer stand throughout and thus the only customers he spoke to were those who had pro-actively approached the stand. He did not recall noticing any negative reaction from any delegate following his conversations with them.

Finally Bayer confirmed that neither representative invited health professionals or selected invitees.

PANEL RULING

The Panel noted that the meeting at issue was arranged by a commercial events company which invited Bayer and one other company to sponsor it. Bayer stated that it had no relationship with the events company other than to provide sponsorship for medical education events. According to Bayer it had no influence over the selection of speakers or the content of the meeting. Neither Bayer nor its representatives had invited guests and it had neither briefed nor entered into a contract with the speaker. The sponsorship invoice referred to meeting costs, speaker fees, room hire and refreshments.

The half day meeting was entitled 'Current Challenges in General Practice' and the agenda referred to two presentations: the first entitled 'IUD/IUS Update Workshop: Putting Contraception into Practice'. The second presentation was in a different therapy area. The front page of the invitation referred to Bayer's sponsorship.

The presentation delivered was entitled 'Intrauterine methods open Surgery' and presented seven patient scenarios and discussed treatment options: A range of devices were referred to including Nova-T380 produced by Bayer.

The first scenario advised that the National Institute for health and Clinical Excellence (NICE) guidance on long-acting reversible contraceptives identified copper devices containing 380mm^2 copper as 'the most effective.' Two devices, Tsafe 380A and TT380 slimline were described as 'WHO gold standard'. A photograph of each device was followed by a slide headed 'Cumulative pregnancy rates' which featured data for a range of devices and Mirena (levonorgestrel+IUD) which was a Bayer product. Subsequent scenarios referred to intrauterine devices produced by other manufacturers. Contrary to Bayer's submission its products were mentioned by brand name.

There was no evidence before the Panel that the commercial events company was acting as Bayer's agent. Nonetheless the Panel did not consider that the arrangements for the meeting were at arm's length as described by Bayer. The Panel noted that the meeting was organised by a commercial events company, featured a presentation in an area of commercial interest for Bayer, was attended by two of its representatives and was partly sponsored by Bayer as set out in the invoice. In such circumstances the Panel considered that it was beholden upon Bayer to ensure that it was an appropriate meeting to sponsor and at the very least that the overall arrangements did not circumvent the requirements of the Code.

The Panel noted its comments about Bayer's role and responsibility in relation to the meeting as described above. The Panel noted that the front page of the invitation was headed at the top with the name of the events company and stated at the bottom of the page that the meeting was sponsored by Bayer Schering Pharma. The Panel considered that the design of the invitation and the declaration of sponsorship was such that Bayer's role was sufficiently clear. No breach of Clause 19.3 was ruled.

Whilst the presentation did mention Bayer's products such references appeared relevant to the scenarios described and the Panel did not consider that there was a disproportionate emphasis on them as alleged. Other products were referred to. In addition the Panel noted that the Code applied, *inter alia*, to the promotion of medicines to health professionals and appropriate administrative staff. Medicines were defined in Clause 1.3 as any branded or unbranded medicine intended for use in humans which requires a marketing authorization. The Code did not apply to the promotion of devices, save where the devices could only be used with a specific medicine. One slide, however, referred to Mirena which was a licensed medicine. Bayer had not submitted that the Code did not apply to the presentation. Irrespective of whether Bayer was responsible for the content of the presentation and taking all the circumstances into account the Panel did not consider that the presentation constituted disguised promotional material and no breach of Clause 12.1 was ruled. Noting its rulings above the Panel consequently ruled no breach of Clauses 9.1 and 2 in this regard.

The Panel noted that in relation to the complainant's allegation about her conversation with a representative the parties' accounts differed. It was difficult in such circumstances to determine precisely where the truth lay. The complainant was anonymous and non contactable. Anonymous complaints were accepted and like all complaints were judged on the evidence provided by the parties. The complainant had the burden of proving their complaint on the balance of probabilities.

The complainant alleged that, following the meeting whilst in conversation with the representative, she had felt undermined, compromised and very intimidated. Bayer, however, submitted that the representative identified by the complainant had spoken to just two delegates before the meeting started and had left by the end of the meeting. The second representative, had remained at the exhibition stand throughout the meeting and thus had only spoken to delegates who proactively approached him. According to Bayer he did not notice a negative reaction from any delegate following their interaction with him.

The Panel noted that great dissatisfaction was usually necessary on the part of a health professional before he/she was moved to submit a complaint. Nonetheless in such circumstances it was impossible to determine where on the balance of probabilities the truth lay. The Panel thus ruled no breach of Clauses 2, 9.1 and 15.2.

Complaint received **15 February 2011**

Case completed **7 April 2011**

CASE AUTH/2387/2/11

PHARMACEUTICAL COMPANY EMPLOYEE v ALK-ABELLÓ

Promotion of Jext

A pharmacist, who worked as a consultant to Lincoln Medical, complained that ALK-Abelló had circulated two documents, a formulary pack and a formulary template for its yet to be launched product Jext (adrenaline auto-injector). Lincoln Medical marketed Anapen (adrenaline auto-injector).

The complainant considered that claims about 'better/longer' shelf life were identical to those for Anapen, ruled to be misleading in Case AUTH/2359/9/10. The complainant thus alleged that the claims for Jext were also misleading.

Further, the complainant alleged that a claim that with Jext 'there is less likelihood of needle stick injury' was unsubstantiated given that Jext was not yet available anywhere in the world and so there was no patient experience of its use. The complainant was advised that there had been no needle stick accident or event with Anapen in the 10 years that it had been licensed and approved in 19 countries.

The detailed response from ALK-Abelló is given below.

The Panel noted that Jext received a marketing authorization on 12 November 2010. The formulary pack and template were distributed for use on 18 and 30 November. The promotion of Jext was after receipt of its marketing authorization and thus no breach of the Code was ruled.

Both documents included details of the shelf life from manufacture (24 months) and this was longer than the other available adrenaline auto-injectors. EpiPen and EpiPen Junior each had a shelf life of 18 months and Anapen Junior of 21 months from the date of manufacture. The documents referred to a potential cost saving of 25% by using Jext instead of EpiPen.

The formulary pack stated that Anapen 300mcg had a shelf life of 24 months from the date of manufacture. Jext and EpiPen cost the same, £28.77. Anapen cost £30.67.

The summary in the formulary pack stated that Jext had a '33% longer shelf-life than EpiPen/EpiPen Jr and 14% longer than Anapen Junior, potentially reducing the number of auto-injectors that a patient has to replace in a lifetime' and referred to the 'longer maximum shelf-life' of Jext vs Epipen in relation to cost savings. Another section headed 'From a PCT perspective' referred to the longer maximum shelf-life'. Page 9 of the formulary pack also referred simply to 'longer maximum shelf-life'. This page included the statement 'It is also conservative to assume the patient has the device for the entire shelf-life from date of manufacture'. References to shelf life also appeared on pages 7 and 10. The Panel noted that it was not always clear, particularly in the summary, that the shelf life was from the date of manufacture.
The Panel did not consider that the claims for Jext were identical to those for Anapen in Case AUTH/2359/9/10 as alleged. In some instances in the present case, Case AUTH/2387/2/11, it was clear that the longer shelf life related to the maximum shelf life from date of manufacture. In the Panel's view 'shelf life' to a customer meant the amount of time they could keep a product before it went out of date. The supply chain was relevant. The Panel considered that the claim in the summary for '33% longer shelf-life …' was misleading. The impression was given that patients would receive Jext with a full 24 months of shelf life and this could not be guaranteed and thus the claim could not be substantiated. Breaches of the Code were ruled.

The Panel noted that neither the previous case, Case AUTH/2359/9/10, nor the material before it now, claimed a better shelf life and this aspect of the current complaint was not considered.

With regard to the claim in the formulary template that with Jext 'there is less likelihood of needle stick injury' the Panel noted the data provided by both parties. ALK-Abelló submitted that the risk of needle stick injury was minimised because after administration a protective shield engaged, locked and covered the needle and thus removed the risk of needle stick injury. Five cases of needle stick injury using EpiPen were reported in 2008-2010. The Panel considered that reducing the risk of needle stick injury would be of interest irrespective of the size of that risk. Given the design of the Jext auto-injector the Panel did not consider that the claim 'there is less likelihood of needle stick injury' was unsubstantiable as alleged. No breach of the Code was ruled.

The Panel noted its rulings outlined above and did not consider that the circumstances warranted a ruling of a breach of Clause 2, which was used as a sign of particular censure and reserved for such use.

A pharmacist who worked as a consultant to Lincoln Medical complained that ALK-Abelló Ltd had circulated two documents, a formulary pack (ref 569AD) and a formulary template (ref 584AD) for its yet to be launched product, Jext (adrenaline tartrate). Copies of the documents were provided.

It had previously been decided that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for inter-company complaints, the employing company would be named in the report. The complainant was advised that this would happen and given the opportunity to withdraw the complaint but he did not do so and the complaint thus proceeded. Lincoln Medical was advised accordingly.

Lincoln Medical marketed Anapen (adrenalin auto-injector).

COMPLAINT

The complainant considered that claims about 'better/longer' shelf life were identical to those for Anapen ruled to be misleading in Case AUTH/2359/9/10. The complainant thus alleged that the claims for Jext were also misleading.

Further, the complainant noted that the Formulary Application Form Template – Jext, in the section headed 'Consequences of not using proposed drug' and repeated on page 4 in the section 'Patient Benefits', there was the claim that with Jext 'there is less likelihood of needle stick injury'. The complainant alleged that this claim was unsubstantiated given that Jext was not yet available anywhere in the world and so there was no patient experience of its use. The complainant had searched the literature and checked with Lincoln Medical and was advised that there had been no needle stick accident or event with Anapen in the 10 years that it had been licensed and approved in 19 countries.

When writing to ALK-Abelló, the Authority asked it to respond in relation to the requirements of Clauses 2, 3.1, 7.2 and 7.4 of the Code.

RESPONSE

ALK-Abelló submitted that Jext 150mcg and Jext 300 mcg received marketing authorizations on 12 November 2010. The two documents in question; Jext Formulary Pack and Jext Formulary Template were certified and approved for first use on 18 November and 29 November 2010 respectively. Both were distributed to the key account managers at ALK-Abelló on 18 and 30 November 2010 to provide pharmacists and senior clinicians in hospital and primary care organisations with the necessary information to facilitate formulary applications for Jext. Therefore ALK-Abelló denied the alleged breach of Clause 3.1 as Jext had been granted a marketing authorization before it started any promotional activity.

ALK-Abelló explained that adrenaline auto-injectors, as with all medicines, had a licensed shelf life from the date of manufacture as stated in the summary of product characteristics (SPC). Clause 3.2 stated 'The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics'.

The Jext Formulary Pack and Jext Formulary Template stated that Jext had a maximum shelf life of 24 months from date of manufacture, a claim that was consistent with the particulars listed in the SPC. Further, both documents also stated that EpiPen and EpiPen Junior (Dey Pharma) had a maximum shelf life of 18 months, Anapen 300/Anapen 500 a maximum shelf life of 24 months and Anapen Junior a maximum shelf life of 21 months. All comparisons were consistent with the individual products' SPCs.

The claims about shelf life in Case AUTH/2359/9/10 were ruled to be misleading and not capable of substantiation because they referred to the unequivocal claim 'Anapen auto-injectors have a longer shelf life than Epipen'. The document ruled in breach of Clauses 7.2 and 7.4 referred simply to shelf life and not maximum shelf life from date of manufacture or indeed licensed shelf life as noted by the Panel.

ALK-Abelló denied the alleged breaches of Clauses 7.2 and 7.4 as it was made very clear that the comparisons referred to the maximum shelf life from date of manufacture of the products as stated in their SPCs. It was further stated in the materials that it was conservative to assume that the patient had the device for the entire shelf life from date of manufacture.

A comparison using maximum shelf life from date of manufacture was appropriate as this was the most conservative measure of the benefit of the additional 6 months' maximum shelf life of Jext compared with EpiPen in a cost minimisation comparison.

Therefore, ALK-Abelló considered that all claims about shelf life in the Jext Formulary Pack and Jext Formulary Template were accurate, balanced and fair. The material was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of Jext and all claims and comparisons were consistent with the products' SPCs and, as such, could be substantiated.

ALK-Abelló explained that needle stick injury was defined as 'an accidental puncture of the skin with an unsterilized instrument'.

ALK-Abelló noted that following administration of EpiPen and Anapen the used needle remained exposed. Exposed needles presented a risk of needle stick injury not only to the patient but also to health professionals and carers, such as paramedics, school staff and parents. Being able to effectively manage the risk of such injuries and their possible consequences was ideal, however small the risk, and

was recognised in a recent EU directive. Clause 6 of Council Directive 2010/32/EU stated workers' exposure must be eliminated by providing medical devices incorporating safety-engineered protection mechanisms. With Jext the risk of needle stick injury was minimised because after administration a protective shield engaged, locked and covered the needle and removed the risk of needle stick injury.

Needle stick injury with used adrenaline auto-injectors represented a small but definite risk. Five cases of needle stick injury using EpiPen in the UK were reported to the marketing authorization holder in the period 2008-2010. Review of the case narratives shows that all incidents would have been prevented by the built in locking needle shield of Jext. This represented approximately 10% of accidental injuries with EpiPen reported during this period which was consistent with the number of reported incidents disposing of a used adrenaline auto-injector in the Medwatch database in the US.

Part of the release specification of Jext was that the locking needle shield was able to resist more than 100N of applied force for more than ten seconds. Short of deliberately disassembling Jext, it was impossible to access the needle after injection.

ALK-Abelló therefore denied the alleged breach of Clause 7.4 as the claim 'there is less likelihood of needle stick injury' could be substantiated.

ALK-Abelló strongly denied the alleged breach of Clause 2 as it had always maintained high standards of ethical promotion of Jext. The company did not believe that at any stage any of its activities or materials had brought discredit upon the pharmaceutical industry.

PANEL RULING

The Panel noted that Jext received a marketing authorization on 12 November 2010. The formulary pack and template were distributed for use on 18 and 30 November. The promotion of Jext was after receipt of its marketing authorization and thus no breach of Clause 3.1 was ruled.

Both documents included details of the shelf life from manufacture (24 months) and this was longer than the other available adrenaline auto-injectors. EpiPen and EpiPen Junior each had a shelf life of 18 months and Anapen Junior of 21 months from the date of manufacture. The documents referred to a potential cost saving of 25% by using Jext instead of EpiPen.

The formulary pack stated that Anapen 300mcg had a shelf life of 24 months from the date of manufacture. Jext and EpiPen cost the same, £28.77. Anapen cost £30.67.

The summary in the formulary pack stated that Jext had a '33% longer shelf-life than EpiPen/EpiPen Jr and 14% longer than Anapen Junior, potentially reducing the number of auto-injectors that a patient has to replace in a lifetime' and referred to the 'longer maximum shelf-life' of Jext vs Epipen in relation to cost savings. Another section headed 'From a PCT perspective' referred to 'The longer maximum shelf-life'. Page 9 of the formulary pack also referred simply to 'longer maximum shelf-life'. This page included the statement 'It is also conservative to assume the patient has the device for the entire shelf-life from date of manufacture'. References to shelf life also appeared on pages 7 and 10. The Panel noted that it was not always clear, particularly in the summary, that the shelf life was from the date of manufacture.

The Panel did not consider that the claims for Jext were identical to those for Anapen in Case AUTH/2359/9/10 as alleged. In some instances in the present case, Case AUTH/2387/2/11, it was clear that the longer shelf life related to the maximum shelf life from date of manufacture. In the Panel's view 'shelf life' to a customer meant the amount of time they could keep a product before it went out of date. The supply chain was relevant. The Panel considered that the claim in the summary for '33% longer shelf-life …' was misleading. The impression was given that patients would receive Jext with a full 24 months of shelf life and this could not be guaranteed and thus the claim could not be substantiated. A breach of Clause 7.2 and 7.4 was ruled.

The Panel noted that neither the previous case, Case AUTH/2359/9/10 nor the material before it now claimed a better shelf life and this aspect of the current complaint was not considered.

With regard to the claim in the formulary template that with Jext 'there is less likelihood of needle stick injury' the Panel noted the data provided by both parties. ALK-Abelló submitted that the risk of needle stick injury was minimised because after administration a protective shield engaged, locked and covered the needle and removed the risk of needle stick injury. Five cases of needle stick injury using EpiPen were reported in 2008-2010.

The Panel considered that reducing the risk of needle stick injury would be of interest irrespective of the size of that risk. Given the design of the Jext auto-injector the Panel did not consider that the claim 'there is less likelihood of needle stick injury' was unsubstantiable and unsupported due to lack of patient experience of its use as alleged. No breach of Clause 7.4 was ruled.

The Panel noted its rulings above and did not consider that the circumstances warranted a ruling of a breach of Clause 2, which was used as a sign of particular censure and reserved for such use.

Complaint received **15 February 2011**

Case completed **4 April 2011**

CASE AUTH/2388/2/11

JOHNSON & JOHNSON/DIRECTOR v GLAXOSMITHKLINE CONSUMER HEALTHCARE

NiQuinin leavepiece

Johnson & Johnson complained about a leavepiece for NiQuitin 21mg Clear Patch (nicotine replacement therapy (NRT)) issued by GlaxoSmithKline Consumer Healthcare. The NiQuitin patch was to be applied for 24 hours. As the complaint involved an alleged breach of undertaking that aspect was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

The front cover of the leavepiece referred to the technology of the NiQuitin Patch which enabled a rapid delivery of nicotine on application and then a steady stream throughout the day.

Page 2 was headed 'NiQuitin 21mg Clear Patch, delivers more nicotine than 25mg/16-hour patch' beneath which was a graph comparing the mean adjusted plasma nicotine against time for NiQuitin 21mg patch and '25mg/16 hour patch'. The claim 'NiQuitin 21mg Clear Patch delivered 57% more nicotine than the 25mg/16-hour patch: [area under the curve] AUC 0-_{00} ($p<0.0001$)' appeared on the bottom of the page. This page was referenced to data on file and to DeVeaugh-Geiss (2010).

Page 3 was headed 'It also delivers more than:' above a graph comparing the plasma nicotine concentration from once daily applications of NiQuitin 21mg patch 24 hour, Nicotinell 21mg patch 24 hour and Nicorette 15mg patch 16 hour over 72 hours from initial dosing. The graph was adapted from Fant *et al* (2000). The claim which accompanied the graph, 'NiQuitin 21mg Clear Patch delivered significantly more nicotine than either of the other patches ($p<0.05$)' was also referenced to Fant *et al*. A second claim 'With NiQuitin 21mg Clear Patch, steady state is reached after the second dose. Steady state maximum concentrations are approximately 30% higher than on day one' was referenced to the NiQuitin 21mg Clear Patch summary of product characteristics (SPC).

Page 4, the back cover, included the prescribing information and was headed 'NiQuitin 21mg Clear Patch delivers more nicotine than 25mg/16-hour patch'.

Johnson & Johnson stated that the leavepiece, which detailed direct pharmacokinetic comparisons of the NiQuitin 21mg Clear Patch with other NRT patches including Nicorette Invisi 25mg Patch (nicotine) and Nicorette 15mg Patch (nicotine), was distributed to prescribing and non-prescribing health professionals.

The primary message of the leavepiece, was that the NiQuitin 21mg patch delivered more nicotine than the Nicorette 25mg patch. This was reinforced by the comparative graph underneath the heading which showed that the NiQuitin 21mg patch had a higher AUC than the Nicorette 25mg patch. The reader was likely to be left with the impression that the NiQuitin patch had a more favourable pharmacokinetic profile or was clinically superior compared with the Nicorette patch. This was likely to influence the prescribing decision, although there was no evidence of superiority. Johnson & Johnson believed that it was inappropriate to show comparative pharmacokinetic data in isolation, in an attempt to influence a prescriber's decision, without it being supported by relevant clinical and safety data.

Johnson & Johnson queried why GlaxoSmithKline Consumer Healthcare would develop a leavepiece which presented comparative pharmacokinetic data which had not been established to translate into clinical difference, unless it was to imply clinical superiority.

In inter-company dialogue, GlaxoSmithKline Consumer Healthcare had stated that health professionals were confused about the delivery of nicotine from the Nicorette 25mg patch and the NiQuitin 21mg patch. This suggested that the leavepiece at issue was intended to address this misconception by informing health professionals of the pharmacokinetic profiles of both products to allow them to make an informed decision. However the presentation of the pharmacokinetic data must comply with the Code and previous undertakings given, and in Johnson & Johnson's opinion, GlaxoSmithKline Consumer Healthcare had not ensured this. Furthermore, it was likely that the way in which the pharmacokinetic data had been presented would confuse health professionals more as only part of the overall story had been told with the remainder being left open to interpretation by the health professional ie the fact that no differences in clinical outcomes between 24 and 16 hour patches had been demonstrated. Presenting the comparative pharmacokinetic profiles in isolation did not help health professionals make an 'informed decision'.

Johnson & Johnson noted that in Case AUTH/2298/2/10 it had similarly alleged that the presentation of single and multiple dose pharmacokinetic profiles had falsely implied clinical superiority in terms of quit rates for NiQuitin

compared with Nicorette patches.

Johnson & Johnson believed that the material now at issue was not consistent with the ruling in Case AUTH/2298/2/10 in which the Panel considered that 'the leaflet was misleading as alleged on this point; it implied the differences in pharmacokinetic profiles led to differences in quit rates and this had not been proven'.

The detailed submission from GlaxoSmithKline Consumer Healthcare is given below.

The Panel noted that there was no mention of clinical outcome data in the leavepiece in question. In the Panel's view the leavepiece was sufficiently different to the mailing at issue in Case AUTH/2298/2/10 which had included pharmacokinetic data and clinical data regarding short- and long-term quit rates such that there appeared to be a consequential link between the two. Thus the Panel considered that GlaxoSmithKline Consumer Healthcare had not failed to comply with its undertaking in Case AUTH/2298/2/10 and no breach of the Code was ruled.

The Panel noted GlaxoSmithKline Consumer Healthcare's concern that since the launch of the Nicorette Invisi 25mg Patch, health professionals believed that the 25mg patch would deliver higher plasma nicotine levels than the NiQuitin 21mg Patch. In the Panel's view it was not unreasonable for GlaxoSmithKline Consumer Healthcare to inform them that this was not so.
The Panel noted that the clear message from the leavepiece was that the NiQuitin 21mg patch delivered more nicotine than the Nicorette 25mg patch. Market research had shown that the majority of prescribers preferred the 25mg patch because of its strength and/or thought that it delivered more nicotine than the NiQuitin 21mg patch. The graph and the claims in the leavepiece sought to reverse that thinking. Although the leavepiece did not refer to any clinical data, it also did not state that the pharmacokinetic differences highlighted and quantified had not been shown to result in any difference in clinical outcome ie quit rate. In the Panel's view, prescribers might now regard the NiQuitin 21mg patch as 'stronger' than the 25mg patch and thus assume that it was clinically more effective. There was no evidence that this was so. This was similarly the case for the graph on page 3 of the leavepiece which compared the pharmacokinetic data for NiQuitin 21mg with that for two other NRT patches. The Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation (2008) stated that indirect comparison failed to detect evidence of a difference in effect between the 16 hour and 24 hour patches. The Panel considered that the leavepiece gave a misleading impression as to the relative clinical efficacy of NiQuitin 21mg clear patch vs the 25mg patch as alleged and a breach of the Code was ruled.

Johnson & Johnson Limited complained about a four page leavepiece (ref NCQ/SYN/KG/0610/02) for NiQuitin 21mg Clear Patch (nicotine replacement therapy (NRT)) issued by GlaxoSmithKline Consumer Healthcare. The NiQuitin patch was to be applied for 24 hours. Inter-company dialogue had failed to resolve all of the issues. As the complaint involved an alleged breach of undertaking that aspect was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

Page 1 of the leavepiece, the front cover, provided details of the technology behind the design of the NiQuitin 21mg Clear Patch which enabled it to provide nicotine in two stages; first a rapid delivery on application and then a steady stream of nicotine throughout the day.

Page 2 was headed 'NiQuitin 21mg Clear Patch, delivers more nicotine than 25mg/16-hour patch' beneath which was a graph comparing the mean adjusted plasma nicotine against time for NiQuitin 21mg patch and '25mg/16 hour patch'. The claim 'NiQuitin 21mg Clear Patch delivered 57% more nicotine than the 25mg/16-hour patch: AUC [area under the curve] 0-00 ($p<0.0001$)' appeared on the bottom of the page. This page was referenced to data on file and to DeVeaugh-Geiss (2010).

Page 3 was headed 'It also delivers more than:' followed by a graph comparing the plasma nicotine concentration from once daily applications of NiQuitin 21mg patch 24 hour, Nicotinell 21mg patch 24 hour and Nicorette 15mg patch 16 hour over 72 hours from initial dosing. The graph was adapted from Fant *et al* (2000). The claim which accompanied the graph, 'NiQuitin 21mg Clear Patch delivered significantly more nicotine than either of the other patches ($p<0.05$)' was also referenced to Fant *et al*. A second claim 'With NiQuitin 21mg Clear Patch, steady state is reached after the second dose. Steady state maximum concentrations are approximately 30% higher than on day one' was referenced to the NiQuitin 21mg Clear Patch summary of product characteristics (SPC).

Page 4, the back cover, included the prescribing information and was headed 'NiQuitin 21mg Clear Patch delivers more nicotine than 25mg/16-hour patch'.

COMPLAINT

Johnson & Johnson stated that the leavepiece, which detailed direct pharmacokinetic comparisons of the NiQuitin 21mg Clear Patch with other NRT patches including Nicorette Invisi 25mg Patch (nicotine) and Nicorette 15mg Patch (nicotine), was distributed to prescribing and non-prescribing health professionals.

The primary message of the leavepiece, as stated in the heading on page two, was that the NiQuitin 21mg patch delivered more nicotine than the Nicorette 25mg patch. However, Johnson &

Johnson believed that the overall impression was that NiQuitin had a 'superior' pharmacokinetic profile, and/or that the pharmacokinetic profile of the NiQuitin patch conferred a clinical advantage over the Nicorette patch. This was reinforced by the comparative graph underneath the heading which showed that the NiQuitin 21mg patch had a higher AUC than the Nicorette 25mg patch. Although the reader was likely to be left with the impression that the NiQuitin patch had a more favourable pharmacokinetic profile or was clinically superior compared with the Nicorette patch, there was no evidence to support this.

Johnson & Johnson believed that prescribers would consider that the comparative pharmacokinetic profiles were meaningful, and that because the data showed that the NiQuitin 21mg patch delivered more nicotine, it was therefore also clinically superior. This was likely to influence the prescribing decision, although there was no evidence of superiority. Johnson & Johnson believed that it was inappropriate to show comparative pharmacokinetic data in isolation, in an attempt to influence a prescriber's decision, without it being supported by relevant clinical and safety data. On balance, Johnson & Johnson believed GlaxoSmithKline Consumer Healthcare asked prescribers to decide purely on relative pharmacokinetic profiles of the patches, where this had not been shown to be directly relevant.

Although the leavepiece included pharmacokinetic data, there was no information relating to the clinical implications of this and also GlaxoSmithKline Consumer Healthcare had made no attempt to interpret the data in order to provide a health professional with a reason to prescribe this product. Johnson & Johnson queried why GlaxoSmithKline Consumer Healthcare would develop a leavepiece which presented comparative pharmacokinetic data which had not been established to translate into clinical difference, unless it was to imply clinical superiority.

In Johnson & Johnson's opinion, the overall impression of this leavepiece was similar to that of the NiQuitin leavepiece at issue in Case AUTH/2298/2/10. In that case Johnson & Johnson alleged that the presentation of the data implied clinical superiority in terms of smoking cessation outcomes for NiQuitin vs Nicorette patches. The use of the graphs showing higher plasma levels in terms of single and multiple dose pharmacokinetic profiles compared with other NRT patches implied superiority in terms of clinical efficacy.

In relation to the leavepiece now at issue GlaxoSmithKline Consumer Healthcare had informed Johnson & Johnson that health professionals were confused about the delivery of nicotine from the Nicorette 25mg patch and the NiQuitin 21mg patch. GlaxoSmithKline Consumer Healthcare's response suggested that the leavepiece was intended to address this misconception by informing health professionals of the pharmacokinetic profiles of both products to allow them to make an informed decision. However, even if GlaxoSmithKline Consumer Healthcare believed this was true, the presentation of the pharmacokinetic data in this leavepiece must comply with the Code and previous undertakings given, and in Johnson & Johnson's opinion, GlaxoSmithKline Consumer Healthcare had not ensured this. Furthermore, it was likely that presentation of the pharmacokinetic data in this way would further serve to increase confusion amongst health professionals as this only provided part of the overall story and left the remainder open to interpretation by the health professional ie the fact that no differences in clinical outcomes between 24 and 16 hour patches had been demonstrated. Presenting the comparative pharmacokinetic profiles in isolation did not help health professionals make an 'informed decision' as GlaxoSmithKline Consumer Healthcare had suggested.

GlaxoSmithKline Consumer Healthcare had referred to the Panel's ruling in Case AUTH/2298/2/10 in which the Panel acknowledged the value of using pharmacokinetic data and stated that '… whilst pharmacokinetic data was useful such data must not be presented in a way that implied consequential clinical benefits unless a direct link between the two had been established'.

GlaxoSmithKline Consumer Healthcare had believed that pharmacokinetic data was useful on this occasion to address the misconception about delivery of nicotine. However, Johnson & Johnson believed that GlaxoSmithKline Consumer Healthcare's presentation of the data was not consistent with the ruling in Case AUTH/2298/2/10 in which the Panel also considered that 'the leaflet was misleading as alleged on this point; it implied the differences in pharmacokinetic profiles led to differences in quit rates and this had not been proven'.

The average prescriber would consider that the comparative pharmacokinetic profiles actually showed a different meaning to that which GlaxoSmithKline Consumer Healthcare attempted to demonstrate. The data presented showed that the NiQuitin 21mg patch delivered more nicotine, and so implied that the NiQuitin patches were pharmacokinetically or clinically superior. However, it had not been established that a 24-hour patch which delivered more nicotine than a 16-hour patch, conferred any clinical benefit whatsoever. It was yet to be established as to whether the break in nicotine dosing overnight provided by a 16-hour patch had any impact on overall efficacy. It was conceivable that the relative difference between the minimal nicotine levels in the morning and higher levels throughout the day, provided by a 16-hour patch, could have a bearing on efficacy. The Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation (2008) stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with

similar point estimates and overlapping confidence intervals in the two subgroups[1]'.

In summary, Johnson & Johnson believed that the comparative pharmacokinetic data presented in the leavepiece over-emphasised the importance of pharmacokinetic data in this context and implied a meaningful advantage for the NiQuitin 21mg patch over and above the Nicorette 25mg patch, which could not be supported. The impression for prescribers would be that the product would also produce better clinical outcomes, which had not been proven. Johnson & Johnson therefore alleged a breach of Clause 7.2.

Although Johnson & Johnson acknowledged that GlaxoSmithKline Consumer Healthcare had amended the data presented following the outcomes and conclusion of Case AUTH/2298/2/10, the same comparative data was presented in the leavepiece at issue and the graphs remained similar. No clinical data was presented within the leavepiece to demonstrate that nicotine plasma levels or differences in pharmacokinetic profiles had a direct bearing on clinical efficacy.

A breach of the Code was ruled in Case AUTH/2298/2/10 and the Panel provided clarity that pharmacokinetic data must not be presented such as to imply consequential clinical benefits unless a direct link between the two had been established. The material at issue was ruled in breach of the undertaking given in Case AUTH/1253/11/01.

The leavepiece now in question was produced as a direct replacement for that found in breach in Case AUTH/2298/2/10 and Johnson & Johnson understood that, following inter-company correspondence in that case, GlaxoSmithKline Consumer Healthcare reviewed its standard operating procedures for the approval of promotional materials. As the leavepiece now in question gave the same overall impression, Johnson & Johnson believed this also represented a further breach of undertaking and therefore alleged a breach of Clause 25. As previously stated, Johnson & Johnson believed this constituted a second breach of the original undertaking made by GlaxoSmithKline Consumer Healthcare in relation to Case AUTH/1253/11/01.

When writing to GlaxoSmithKline Consumer Healthcare, the Authority asked it to respond to Clause 2 in relation to the alleged breach of undertaking in addition to Clause 25 as cited by Johnson & Johnson.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that traditionally, the starting dose for NRT patches had been either 21mg (worn for 24 hours) or 15mg (worn for 16 hours). Johnson & Johnson introduced its 25mg patch in 2009. Unsurprisingly, health professionals believed that the 25mg patch would deliver more nicotine to the bloodstream than a 21mg patch. This misconception was confirmed by anecdotal feedback from the representatives, and by market research conducted by GlaxoSmithKline Consumer Healthcare. The market research carried out on 12 and 13 January 2011 showed that when asked 'Which of the following patches delivers more nicotine?' 71% of GPs and 78% of practice nurses chose Nicorette 25mg over NiQuitin or Nicotinell 21mg patches. Sixty per cent of respondents who used a 25mg patch for patients who smoked more than 20 cigarettes a day, cited strength as the reason why they prescribed the product and 28% that it delivered more nicotine. From the representative feedback and the market research it was clear that the majority of health professionals believed the Nicorette 25mg patch delivered more nicotine than the NiQuitin 21mg patch and a substantial proportion prescribed it for this reason. However, as the results of the head-to-head study showed, NiQuitin 21mg delivered the most nicotine, not Nicorette 25mg. Thus it was important that health professionals knew about the data so they could make informed and rational treatment decisions. If they wanted to prescribe the patch that delivered the most nicotine, then they should prescribe NiQuitin 21mg rather than Nicorette 25mg.

That NiQuitin 21mg delivered more nicotine than Nicorette 25mg might seem counter-intuitive based on the product labelling. However, Johnson & Johnson and GlaxoSmithKline Consumer Healthcare used different technologies of patch manufacture and based their labelled strength on different methods of calculation. GlaxoSmithKline Consumer Healthcare labelled its patch according to the amount of nicotine actually delivered to the bloodstream, whereas Johnson & Johnson labelled its patch according to the 'average amount of nicotine released over 16 hours'.

In July 2008 GlaxoSmithKline Consumer Healthcare contacted the Medicines and Healthcare products Regulatory Agency (MHRA) regarding the difference in nomenclature of the transdermal patches, specifically that different companies used different methodologies to calculate their labelled dose. The MHRA acknowledged the inconsistent approach and whilst companies were not required to align, it hoped that the industry would be able to reach a harmonised position. However, no progress had been made in this regard. The inconsistency had not impacted prescribers until the introduction of the 25mg patch and the consequential assumption that it was the strongest/highest strength/delivered most nicotine. GlaxoSmithKline Consumer Healthcare was keen to ensure that prescribers made informed prescribing decisions based on robust evidence and therefore it needed to address the misconception that the Nicorette 25mg patch delivered more nicotine than the NiQuitin 21mg patch.

GlaxoSmithKline Consumer Healthcare regarded undertakings to the PMCPA extremely seriously and was concerned that the leavepiece should be

fundamentally different from the material found in breach in Cases AUTH/2298/2/10 and AUTH/1253/11/01, and comply with previous advice by removing any reference to comparative clinical benefits. The leavepiece simply presented the pharmacokinetic data and made no clinical benefit claims. It informed health professionals that NiQuitin 21mg delivered more nicotine than Nicorette 25mg, Nicorette 15mg and Nicotinell 21mg, and graphically displayed the nicotine levels in two separate head-to-head studies. In the previous cases pharmacokinetic data had been presented in the same item as data which discussed quit rates and the Panel noted that, although pharmacokinetic data was useful, it must not imply consequential clinical benefits unless a direct link between the two had been established. In the most recent case (Case AUTH 2298/2/10) GlaxoSmithKline Consumer Healthcare believed that it had separated the quit rate data from the pharmacokinetic data by putting it on separate pages, but the Panel considered by highlighting the NiQuitin quit rates this implied an advantage for NiQuitin, especially as there was also a claim that no other patch had been found to be more effective. Consequently, in producing the leavepiece now at issue GlaxoSmithKline Consumer Healthcare took the undertakings seriously and removed all reference to clinical outcomes to ensure compliance.

Johnson & Johnson agreed that the primary message of the leavepiece was that the NiQuitin 21mg patch delivered more nicotine than the Nicorette 25mg patch, but believed that the overall impression was that NiQuitin 21mg had a superior pharmacokinetic profile and/or the pharmacokinetic profile offered a clinical advantage over the Nicorette 25mg patch. On the contrary, the leavepiece was clear and unambiguous in its message – the NiQuitin 21mg patch delivered more nicotine than the Nicorette 25mg patch and it also delivered more than the Nicotinell 21mg and Nicorette 15mg patches. The pharmacokinetic claims were factual and highlighted only one pharmacokinetic parameter – that of dose delivered – as there was a clear need to educate health professionals in this regard. There were no claims of pharmacokinetic superiority or implications of clinical superiority.

It was important that health professionals saw the data as generated in these two head-to-head studies so that they could have an informed opinion and base their treatment decisions on evidence rather than assumption. Each of the pharmacokinetic profiles displayed in the graphs were different, and one was not necessarily superior over the others as there were many different elements that made up a pharmacokinetic profile. One person's superior pharmacokinetic profile was another's inferior. Aspects of one profile might be considered more beneficial to some health professionals than others. For years Nicorette had promoted the benefits of not delivering nicotine overnight and this could be seen in the substantial decline in overnight nicotine levels for the 25mg patch plotted clearly in the graph on page 2 and also for the 15mg patch in the graph on page 3. Conversely, the 24-hour patches both maintained significant overnight nicotine levels. For health professionals who preferred patches that did not maintain overnight nicotine levels, then the NiQuitin 21mg patch pharmacokinetic profile was clearly not superior.

The leavepiece was specifically designed to disabuse health professionals of the understandable misconception that the Nicorette 25mg patch delivered more than the NiQuitin 21mg patch. A standard treatment course of the Nicorette 25mg patch cost 20% more than a standard treatment course of the NiQuitin 21mg patch, but many health professionals prescribed or recommended the Nicorette 25mg patch because they assumed that they got more nicotine for their money; the pharmacokinetic data demonstrated that this was not so.

GlaxoSmithKline Consumer Healthcare refuted the allegation that the comparative pharmacokinetic data over-emphasised the importance of pharmacokinetic data and implied a meaningful advantage for NiQuitin 21mg over Nicorette 25mg. The leavepiece was used to correct the widespread misconception that the Nicorette 25mg patch delivered more nicotine than the NiQuitin 21mg patch. It was accurate, factual, unambiguous and not misleading. It made no claims for clinical outcomes and did not claim or imply superiority of pharmacokinetic profile. It was simply a presentation of the direct head-to-head pharmacokinetic data. GlaxoSmithKline Consumer Healthcare did not believe it had breached Clause 7.2.

GlaxoSmithKline Consumer Healthcare was confident it had not breached any undertakings previously given. This leavepiece was fundamentally different from previous items found in breach which discussed both pharmacokinetic data and clinical outcome data. The leavepiece discussed pharmacokinetic data only and no direct or indirect reference was made to relative clinical benefits. Thus GlaxoSmithKline Consumer Healthcare refuted the alleged breach of Clause 25 and as such also refuted the allegation of a breach of Clause 2.

PANEL RULING

The Panel noted that there was no mention of clinical outcome data in the leavepiece in question. In the Panel's view the leavepiece was sufficiently different to the mailing at issue in Case AUTH/2298/2/10 which had included pharmacokinetic data and clinical data regarding short- and long-term quit rates such that there appeared to be a consequential link between the two. Thus the Panel considered that GlaxoSmithKline Consumer Healthcare had not failed to comply with its undertaking in Case AUTH/2298/2/10 and no breach of Clause 25 was ruled.

The Panel also ruled no breach of Clause 2 in this regard.

The Panel noted GlaxoSmithKline Consumer Healthcare's concern that since the launch of the Nicorette Invisi 25mg Patch, health professionals believed that the 25mg patch would deliver higher plasma nicotine levels than the NiQuitin 21mg Patch. In the Panel's view it was not unreasonable for GlaxoSmithKline Consumer Healthcare to inform them that this was not so. Page 2 of the leavepiece was headed 'NiQuitin 21mg Clear Patch delivers more nicotine than 25mg/16 hour patch' and the graph below depicted a greater AUC for NiQuitin than the 25mg patch. A claim below the graph quantified the additional nicotine delivered by the NiQuitin patch vs the 25mg patch (57%, $p<0.0001$).

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that its patch was labelled according to the amount of nicotine delivered to the bloodstream whereas the Nicorette patch was labelled according to 'the average amount' of nicotine released over 16 hours. This was not clear in the material at issue.

The Panel noted that the clear message from the leavepiece was that the NiQuitin 21mg patch delivered more nicotine than the Nicorette 25mg patch. Market research had shown that 60% (n=40) of prescribers preferred the 25mg patch because of its strength and out of 151 prescribers, 74% (n=111) thought that it delivered more nicotine than the NiQuitin 21mg patch. The graph and the claims in the leavepiece sought to reverse that thinking. Although the leavepiece did not refer to any clinical data, it also did not state that the pharmacokinetic differences highlighted and quantified had not been shown to result in any difference in clinical outcome ie quit rate. In the Panel's view, prescribers might now regard the NiQuitin 21mg patch as 'stronger' than the 25mg patch and thus assume that it was clinically more effective. There was no evidence that this was so. This was similarly the case for the graph on page 3 of the leavepiece which compared the pharmacokinetic data for NiQuitin 21mg with that for the Nicotinell 21mg/24 hour patch and the Nicorette 15mg/16 hour patch. The Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that indirect comparison failed to detect evidence of a difference in effect between the 16 hour and 24 hour patches. The Panel considered that the leavepiece gave a misleading impression as to the relative clinical efficacy of NiQuitin 21mg clear patch vs the 25mg patch as alleged and a breach of Clause 7.2 was ruled.

Complaint received **16 February 2011**

Case completed **19 April 2011**

CODE OF PRACTICE REVIEW – May 2011

Cases in which a breach of the Code was ruled are indexed in **bold type.**

2333/7/10	**Anonymous v Bayer**	**Promotion of Levitra**	**Breach Clause 4.1** **Recovery of item required by Appeal Board** **Audit required by Appeal Board** **Public reprimand by Appeal Board** **Further Audit required by Appeal Board**	**No appeal** **Report from Panel to Appeal Board**	**Page 3**
2352/8/10	**GlaxoSmithKline v Chiesi**	**Clinical Support Service**	**Breaches Clauses 2, 9.1 and 18.4**	**Appeal by respondent**	**Page 9**
2362/10/10	**Boehringer Ingelheim v Novartis**	**Promotion of Onbrez**	**Five Breaches Clause 7.2 Breaches Clauses 7.4 and 7.10**	**No appeal**	**Page 24**
2366/10/10	**Ex-employee v Lilly**	**Conduct of representatives and meeting arrangements**	**Breach Clause 2 Two breaches Clauses 9.1 and 15.2 Breach Clause 19.1**	**Appeal by complainant**	**Page 31**
2367/10/10	**Doctor v Takeda**	**Use of inverted black triangle**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 39**
2369/11/10	**Abbott Healthcare v Genus**	**Promotion of APO-go**	**Three Breaches Clause 7.2 Four Breaches Clause 7.9 Breaches Clauses 9.1, 22.1 and 22.2**	**No appeal**	**Page 44**
2370/11/10	Anonymous employee v Sanofi-Aventis	Alleged excessive hospitality	No Breach	No appeal	Page 50
2371/11/10	Former employee v Astellas	Promotional Practices	No Breach	No appeal	Page 54
2372/11/10	**Former employee v Alcon**	**Promotion of Travatan**	**Breaches Clause 3.1 9.1 and 15.9**	**No appeal**	**Page 61**
2373/11/10	**Doctor v Sanofi-Aventis**	**Special report in journal**	**Breach Clause 12.1**	**No appeal**	**Page 67**
2377/12/10	**Novo Nordisk v Merck Sharp & Dohme**	**Promotion of Janumet**	**Three Breaches Clause 7.2 Breach Clause 7.3 Two Breaches Clause 7.4**	**Appeal by respondent**	**Page 70**

2379/1/11	**Anonymous v Chiesi**	**Promotion of Fostair**	**Breaches Clauses 3.2,7.2 and 7.10**	**No appeal**	**Page 78**
2383/2/11	**Anonymous General Practitioner v Bayer**	**Yasmin journal advertisement**	**Breaches Clauses 2 3.2,7.2 and 7.9**	**No appeal**	**Page 81**
2386/2/11	Anonymous v Bayer	Meeting arrangements and conduct of a representative	No Breach	No appeal	Page 87
2387/2/11	**Pharmaceutical company employee v Alk Abelló**	**Promotion of Jext**	**Breaches Clauses 7.2 and 7.4**	**No appeal**	**Page 92**
2388/2/11	**Johnson & Johnson Director v GlaxoSmithKline Consumer Healthcare**	**NiQuitin leavepiece**	**Breach Clause 7.2**	**No appeal**	**Page 95**

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 Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, are always in a majority when matters are considered by the Appeal Board.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY

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