NUMBER 67 FEBRUARY 2010

CODE OF PRACTICE REVIEW

PMCPA Prescription Medicines Code of Practice Authority

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

COMPLAINTS IN 2009 DOWN ON 2008

In 2009 the PMCPA received 92 complaints as compared with 112 in 2008. There were 127 complaints in 2007, 134 complaints in 2006, 101 in 2005 and 119 in 2004.

There were 87 cases to be considered in 2009, as compared with 103 in 2008. The number of cases usually differs from the number of complaints because some complaints involve more than one company and others do not become cases at all, often because they do not show that there may have been a breach of the Code.

The number of complaints from health professionals in 2009 (40) exceeded the number from pharmaceutical companies (both members and non-members of the ABPI) (24). Complaints made by pharmaceutical companies are generally more complex than those from outside the industry, usually raising a number of issues.

Two complaints were made by members of the public and four by pharmaceutical company employees. There were seven anonymous complaints and one complaint was made by an organisation. Nine of the complaints from health professionals were also anonymous.

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

HELP US TO HELP YOU - MAKING A COMPLAINT

The PMCPA aims to deal with all complaints under the Code in a timely manner. The following is intended to guide complainants so that their submissions will help the Authority in this regard.

Inter-company complaints will only be accepted if they are signed or authorized in writing by the company's managing director, chief executive or equivalent and if inter-company dialogue at a senior level has not been successful (Paragraph 5.2 of the Constitution and Procedure refers). The complainant company must submit a formal statement with its complaint detailing the actions taken. Complainants must state those clauses of the Code which are alleged to have been breached and must not go beyond the scope of the inter-company dialogue. If new matters and/or clauses are raised they will be referred back for discussion between the parties in the first instance. Guidance on inter-company dialogue was published in the May 2009 Code of Practice Review and is also available on the Authority's website (www.pmcpa.org.uk).

When submitting a complaint brevity might not always be possible if complex matters are to be discussed but a clear and precise exposition of the facts should be provided. Repetition of the same point should be avoided. All points should be covered in the letter to the PMCPA. In inter-company complaints cross reference to previous correspondence between the parties should be avoided.

Cite only those clauses of the Code that are most relevant to specific aspects of your complaint. It is often the case that although a number of clauses are alleged to have been breached, some of those allegations

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PUBLIC REPRIMAND FOR SOLVAY HEALTHCARE

Solvay Healthcare Limited has been publicly reprimanded by the Code of Practice Appeal Board for providing grants in the form of cheques via its representative to a GP on four separate occasions to conduct patient audits. The company had no processes to enable it to check that the money was used to pay a nurse to conduct an audit and how long that would take or that the audit itself was appropriate. The nurse employed to undertake the audits had not been assessed by the company with regard to her ability to carry out the task. There was a failure of management.

The Appeal Board noted that there appeared to be a marked consequential increase in the prescribing of Omacor by the GP concerned and it queried whether, as a result, patients had been put at risk.

In addition the Appeal Board required an audit and a subsequent re audit of Solvay's procedures.

Full details can be found at page 3 of this issue of the Review in the Report for Case AUTH/2198/1/09.

PROPOSALS TO AMEND THE CONSTITUTION AND PROCEDURE FOR THE PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY

The consultation on the proposals to amend the Constitution and Procedure for the Prescription Medicines Code of Practice Authority has now closed. The proposed amendments and the explanatory memorandum are available on our website (www.pmcpa.org.uk).

The proposals were sent to the Medicines and Healthcare products Regulatory Agency (MHRA), the British Medical

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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 dates on which places remain available are:
Wednesday, 31 March 2010
Monday, 7 June 2010

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.

HELP US TO HELP YOU - MAKING A COMPLAINT

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will be rejected by the Code of Practice Panel and thus, unless successfully appealed, an administrative charge will be levied against a complainant company. A claim ruled in breach of just one or two clauses of the Code will preclude its future use. It is wise to stick to your strongest argument and cite the most relevant clauses of the Code.

It is quicker to deal with concise complaints. Instead of submitting one very large complaint about a media campaign and material issued to health professionals, consider submitting two smaller complaints, covering each aspect separately. That way if the Panel needs to contact either party for more information on just one aspect of the campaign then at least the other aspect can be dealt with uninterrupted.

Consider giving your complaint to someone who is not familiar with the matters at issue to read to ensure that it clearly sets out a well reasoned argument. When a published paper etc is cited, it should be provided if possible. References should be relevant; there is little merit in merely citing and/or submitting a large number of published papers without any commentary on them. If you are able to provide copies of relevant published papers or other documents please ensure that all pages are provided. It is not unusual for only the odd or even pages to be sent to the Authority.

PROPOSALS TO AMEND THE CONSTITUTION AND PROCEDURE FOR THE PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY

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Association (BMA), the Royal Pharmaceutical Society of Great Britain (RPSGB) and the Royal College of Nursing (RCN) as required by the Constitution and Procedure. The comments will be assessed and formal proposals will be considered by ABPI members shortly.

CODE AWARENESS

The PMCPA delivered a pilot Code awareness roadshow to NHS employees in the North West in January. The aim of the project was to increase awareness and understanding of the Code by health professionals and others working in the NHS to give greater confidence to engage with the industry to benefit patient care. Please visit the PMCPA website for more information on this project.

CASE AUTH/2198/1/09

PRIMARY CARE TRUST v SOLVAY

Patient identification programme

The assistant medical director of a primary care trust (PCT) complained that a service provided to a general practitioner by Solvay had led to the inappropriate prescribing of Omacor (omega 3-acid ethyl esters 90).

The complainant explained that the GP had met the Solvay representative who promoted Omacor. The GP thought that patients would benefit from the medicine and he signed an agreement with Solvay which provided an unconditional financial grant to audit patients with cardiovascular risk factors and review their long term management. The agreement named a nurse who would do the audit. The GP had been introduced to the nurse by the Solvay representative and although he might have been shown a protocol by the nurse no copies were kept and so nothing was known about it. The GP thought the nurse was identifying patients who had a history of cerebrovascular or coronary heart disease or hypertension or abnormal lipids. The nurse had access to the medical records, identified 'suitable' patients and put Omacor on repeat prescriptions. The GP signed the prescriptions and the letters explaining why the medicine was prescribed. The complainant did not know if the GP was offered any inducement.

The complainant submitted that the matter raised concerns about the nurse and the GP; it had also identified issues relating to Solvay's promotion of Omacor. Breaches of the Code were alleged.

The detailed response from Solvay is given below.

The Panel considered that it was not necessarily unacceptable for pharmaceutical companies to sponsor audits in general practice. The supplementary information to the Code prohibited switch programmes but genuine therapeutic reviews which aimed to ensure that patients received optimal treatment following clinical assessment were acceptable. The decision to change or commence treatment must be made for each individual patient by the prescriber and every decision to change an individual's treatment must be documented with evidence that it was made on rational grounds.

The Panel noted Solvay's submission that it had given the GP unconditional grants to audit patients at increased cardiovascular risk to review their therapy between November 2006 and June 2007. Approximately £1,700 had been given to cover the cost of a nurse to do the audits. As part of the agreement the GP was offered template letters to recall patients for review. It was not clear whether all the patients prescribed Omacor following the audit met the licensed indications.

The Panel noted that the details of that audit were unknown to Solvay. It appeared that the company had no way of knowing if it was paying for a clinically robust audit. This was unacceptable. In the Panel's view, pharmaceutical companies sponsoring third parties, particularly individuals, must be reasonably confident that their proposed activities were clinically sound and complied with the Code. In addition to funding and agreeing that the audit be performed by an external healthcare practitioner, Solvay had, in letters to the GP, stated that the audit would be performed by a named nurse. Solvay had, in effect, provided the nurse to do the audit who the company understood had some expertise in similar audits. Again the Panel considered that this was unacceptable; if the company was recommending staff to carry out the audit it should be sure that they had the necessary expertise. In the Panel's view, by introducing the nurse to the practice, Solvay had to assume some responsibility for her actions.

The Panel was concerned about the representative's role. Although Solvay stated that the representative had sought authority for financial support to be given, it appeared that no regional sales manager or healthcare development manager had discussed the project with the GP as recommended in guidance issued to the field force. The representative had provided the GP with the contact details of the nurse and had arranged for the GP to sign the agreement regarding the support to be provided by Solvay. The representative had delivered the cheque which represented the fee to be paid to the nurse for conducting the audit. In the Panel's view the delivery of cheques to doctors by representatives in this way gave a very poor impression; it might be perceived by some to be an inducement to prescribe the company's products given the prime role of a representative was to promote medicines.

The Panel noted Solvay's involvement with the audit and subsequent therapy review and considered that it was inextricably linked to it. The company had given the GP approximately £1,700 but had had no oversight of the protocol; it had, in effect, provided a nurse to do the audit although it appeared to have no evidence that she was suitably experienced to be able to conduct the audit or knowledge of what she was going to do. The Panel considered that the vague arrangements which existed were wholly unacceptable; the arrangements were such that Solvay had no way of ensuring that the grant which it had given to the GP would be used for an appropriate purpose. The Panel considered that the arrangements were such that they did not constitute a bona fide medical and

educational good or service. The Panel ruled a breach of the Code.

The Panel noted that data provided by the complainant showed that the prescribing of Omacor in the practice in question greatly exceeded the prescribing of Omacor in the other practices in the area. The Panel further noted that shortly after receiving each letter from Solvay regarding the provision of more money (November 2006, January, April and June 2007) prescribing of Omacor in the practice in question increased. The Panel also noted the complainant stated that following the meeting with the representative the GP considered his patients would benefit from Omacor and he signed an agreement with Solvay. The Panel noted its concerns about the role of the representative. The Panel considered that on the balance of probabilities the delivery of cheques by a representative in association with an unacceptable service amounted to an inducement to prescribe Omacor in breach of the Code. The Panel had no evidence that the grants constituted the disguised promotion of Omacor. No breach of the Code was ruled in that regard.

The Panel was very concerned about the overall arrangements set out above. The Panel further considered that given its involvement in the process, Solvay's failure to assume any responsibility for the audit which it facilitated meant that the conduct of employees had fallen short of competent care such as to bring discredit upon or reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned that Solvay appeared to have no procedures in place for ensuring that grants given to facilitate general practice audit were spent on valid audits/therapy reviews and the like. The Panel was also concerned that Solvay would recommend third parties to perform the audits/reviews, without knowing their relevant qualifications or experience to perform such tasks, but take no responsibility for their actions. The Panel decided to report Solvay to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. In accordance with Paragraph 7.1 of the Constitution and Procedure, the Panel further required Solvay to suspend the provision of grants for patient identification programmes and the like such that no new agreements were signed.

Solvay accepted all of the Panel's rulings of breaches of the Code.

The Appeal Board was very concerned that Solvay had provided grants in the form of cheques via its representative to the GP on four separate occasions. The Appeal Board considered that it was inappropriate for a representative to hand over money to a doctor. The company had no processes to enable it to check that the money was used to pay a nurse to conduct an audit and how long that would take or that the audit itself was appropriate. Further there was no assessment of the first audit before providing a cheque to the same doctor for the next audit. The Appeal Board did not accept that the payment to the doctor was unconditional as submitted by Solvay. It was provided for a specific reason – ie an audit. The Appeal Board was further concerned that the nurse, introduced to the GP by Solvay and employed by him to undertake the patient identification programme, had not been assessed by the company with regard to her ability to carry out the task for which she was to be paid. There was a failure of management.

The Appeal Board further noted that there appeared to be a marked consequential increase in the prescribing of Omacor by the GP concerned and it queried whether, as a result, patients had been put at risk.

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

Upon receipt of the audit report the Appeal Board noted with concern that some of Solvay's policies still needed to be changed so as to ensure compliance with the Code. The Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require a further audit of Solvay's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in November 2009 when the Appeal Board expected Solvay's standard operating procedures (SOPs) to be completed. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary. In accordance with Paragraph 13.6 of the Constitution and Procedure the Appeal Board decided that an interim case report should be published on the PMCPA website.

Upon receipt of the re-audit report the Appeal Board noted that Solvay had made much improvement since the audit on 5 June 2009. The Appeal Board decided that on the basis that the recommendations from the re audit were either implemented or ongoing no further action was required.

The assistant medical director of a primary care trust (PCT), complained about a patient identification programme sponsored by Solvay Healthcare Limited in 2006.

COMPLAINT

The complainant explained that the PCT had recently investigated inappropriate Omacor (omega

3-acid ethyl esters 90) prescribing in a local general practice. The product was prescribed for 122 patients none of whom met its licensed indications.

The complainant did not know if the doctor was offered any inducement to prescribe Omacor to these patients. Nothing was known about the protocol used by the nurse to identify 'suitable' patients or whether this came from Solvay. There were serious concerns about the professional behaviour of the nurse in relation to this incident, and Solvay's role in introducing her to the practice was unclear.

The complainant provided details of events. The named GP had met the Solvay representative who promoted Omacor. The GP thought that patients would benefit from the medicine and he signed an agreement with Solvay. This provided an unconditional financial grant to audit patients with cardiovascular risk factors and review their long term management. The agreement named a nurse who would do the audit. The GP stated that he had been introduced to the nurse by the Solvay representative and although he might have been shown a protocol by the nurse no copies were kept. The GP thought the nurse was identifying patients who had a history of cerebrovascular or coronary heart disease or hypertension or abnormal lipids. The nurse was given access to the medical records, identified 'suitable' patients and put Omacor on repeat prescriptions. The GP signed the prescriptions and the letters explaining why the medicine was prescribed.

The complainant stated that the nurse selected hypertensives without heart disease and patients with normal triglycerides for treatment with Omacor. A number of nursing concerns were listed by the complainant.

With regard to Solvay the complainant was concerned that the company introduced the nurse to the practice, the nurse recommended by Solvay identified 122 patients as suitable for Omacor when none met the licensed indications, there were concerns about her professional competence and the PCT was unable to obtain a copy of the protocol for review.

The complainant submitted that whilst the findings had raised concerns about the GP, it had also identified issues relating to Solvay's promotion of Omacor. Breaches of Clauses 2, 12, 18.1 and 18.4 of the 2008 edition of the Code were alleged.

* * * * *

Grants to facilitate the patient identification programme at issue had been made in 2006-2007 thus the provisions of the 2006 edition of the Code applied. The requirements of the clauses cited by the complainant had not changed from 2006 to 2008 but there had been some re-numbering so that the equivalent clauses in 2006 were 2, 10, 18.1 and 18.4. This case was considered under the requirements of the 2006 Code using the 2008 Constitution and Procedure.

* * * * *

RESPONSE

Solvay noted that the complaint referred to an unconditional grant which it had made to support a patient identification programme in 2006 at a GP surgery. The company noted that little evidence had been presented to support the allegations against Solvay and the independent nurses who undertook the audit at the request of the GP. Solvay was disappointed that a complaint had been made as it had twice written to the PCT to try to explain the nature of a patient identification programme and the involvement of Solvay in such an audit.

1 Alleged promotion of Omacor outside its licensed indications.

The licensed indications for Omacor were:

> 'Post Myocardial Infarction
> Adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (e.g. statins, anti-platelet medicinal products, beta-blockers, ACE inhibitors).
>
> Hypertriglyceridaemia
> Endogenous hypertriglyceridaemia as a supplement to diet when dietary measures alone are insufficient to produce an adequate response:
> - type IV in monotherapy,
> - type IIb/III in combination with statins, when control of triglycerides is insufficient.'

Solvay noted that from the PCT's report into this incident, of 122 patients alleged to have been prescribed Omacor outside its licensed indication, 23.7% had a past history of myocardial infarction and 71.4% of patients had abnormal levels of triglyceride prior to starting Omacor (section 7 - Identifying patients). Solvay disagreed with the PCT's statement that none of these patients met the licensed indications.

Solvay had always ethically promoted Omacor within its licensed indications. A copy of the Omacor detail aid used in 2006 was provided. The sales team was trained to the highest standards and was fully aware of its obligations under the Code. The representative concerned was very experienced and had been with Solvay for many years. There had been no complaints from either primary or secondary care health professionals in his area about the manner in which Omacor was promoted. Solvay strenuously denied any suggestions that Omacor had been promoted outside its licensed indication; it therefore denied any suggestions of a breach of Clause 3.

2 Alleged inducement

Solvay stated that it provided an unconditional grant to the GP, following a request for help to audit patients at increased cardiovascular risk to review their therapy. Four payments were made to the GP, totalling £1,700, to pay for 64 hours of nurse resource for an audit programme reviewing the cardiovascular risks of his patients. Solvay understood that the audits looked at different areas of cardiovascular risk and analysis of the practice's performance against quality outcome framework (QoF) targets.

Solvay provided the standard operating procedure (SOP) from 2006 for the field force, which defined the management of patient identification programmes. Solvay also enclosed the agreement letter, signed by the GP, which clearly stated that the funding provided was an unconditional grant from Solvay to support an audit of patients with cardiovascular risk factors. The letter clearly stated that no Solvay employee would be involved in the audit, that the nurses conducting the audit were external to Solvay, and that the payments were solely to fund the nurse resource to conduct the audit. Solvay believed that the payments were fair market value for an experienced nurse's time. Solvay therefore denied that these payments were in breach of Clause 18.1.

Similar audits had provided a broad ranging review of cardiovascular patients to identify untreated adverse risk profiles. This would include both lifestyle changes, for example smoking cessation and weight reduction, together with a therapeutic review eg whether patients reached clinically accepted targets for management of hypertension or lipid lowering. The SOP and the signed letter of agreement with the GP required that patients identified during the audit would be subsequently reviewed by the GP for any appropriate clinical decisions. Solvay noted that no other outcomes of the audit, apart from changes in Omacor prescribing, had been investigated or presented in the PCT report.

Nurses, who were independent of Solvay, conducted the audit; there was no formal relationship between the nurses and Solvay. The nurses were not, and never had been, employees of Solvay. The company could not find any records for any payments to the named nurses, suggesting a formal relationship, over the last five years in its detailed financial records. The company was able to provide the names of the nurses involved from the original letters of agreement with the GP. Solvay provided two names and submitted that it understood that they were local practice nurses with some expertise in similar audits. The nurses were employed by the GP directly and any contracts, training and definition of their role and responsibilities would be between them and the practice. In conclusion, Solvay only provided an unconditional grant and in consequence it did not have a protocol nor could it provide any other details of the nurses who conducted the audits.

Solvay was confident that the audit programme managed by the GP was consistent with a genuine therapy review programme as defined in the supplementary information to Clause 18.4. Solvay did not accept that genuine therapeutic review programmes could be considered under Clause 12 as a form of disguised promotion.

Solvay was proud to work in partnership with the NHS and strongly denied that its conduct was in breach of Clause 2.

In response to a request for further information, Solvay submitted that generic template letters were provided to the GP by its medical representative. Examples of these letters were included in the standard operating procedures for the field force.

Neither Solvay nor its employees, including the representative played any role in the composition or production of the patient letter used by the GP. The representative had not previously seen a copy of the patient letter submitted by the complainant or any document resembling it. That letter was plainly entirely different in purpose, content and style to the generic template letters Solvay provided.

In response to the GP's request for assistance (see below), Solvay's representative introduced a nurse by providing her name and telephone number to the doctor. The telephone number Solvay held no longer appeared to be current.

After attending a meeting which discussed the treatment of patients with cardiovascular risk factors, the GP told the representative that he wished to carry out an audit. The GP asked Solvay for financial assistance and logistical support in identifying someone who might be able to help carry out the audit. As regards the logistical support, the representative provided the GP with the telephone number for the nurse and submitted a request to his manager to support the audit financially in accordance with the company's SOP. Authority was given for this financial support. The representative thereafter arranged for the GP to sign the agreement with Solvay and visited the doctor to deliver the cheque representing the fee to be paid to the nurse for her time in conducting the audit.

The representative had no other involvement with the audit; he did not recommend to the GP that he be supported, and did not solicit a request for support from him.

Solvay supported the GP with four audits to identify patients with cardiovascular risk factors between November 2006 and July 2007. Four payments were made totalling £1,700, to pay for a total of 64 hours of audit time. In this context, Solvay noted its earlier reference to the second of two named individuals who it erroneously stated was a nurse in its letter of 29 January 2009, as Solvay understood that she was a practice manager.

Solvay had provided unconditional grants to support patient identification programmes to a number of other medical practices across the UK. More than 320 unconditional grants were made in 2007 and 2008, spread evenly over those two years. Solvay was not aware of any complaints being made about the provision of these grants.

To the best of Solvay's knowledge, given the time available and based on the information which it had obtained from its representative and regional manager, the nurse had been involved in around 12 audits which had been supported by Solvay in 2007/2008. Solvay was attempting to check this against copies of the agreements which it held.

For the sake of clarity, it was important to note that Solvay provided financial support to the GP for a records audit only, which it described as a patient identification programme. The purpose of this exercise was to enable the GP to identify patients with various cardiovascular risk factors. Solvay would expect this to consist purely of a computer and/or paper records search resulting in a list of names. The GP decided how the search would be conducted and what information he wished to extract from his patients' records. Solvay's financial support, and any other involvement, ended at that point.

Solvay had offered the GP, and other doctors, template letters inviting patients identified as a result of the search to see their GP, but it did not know if the GP at issue used Solvay's letters. Solvay did not provide financial or any other support thereafter for any therapeutic review that the GP at issue might decide to conduct following the Solvay supported audit. The agreement with the GP clearly recorded the distinction between the audit supported by Solvay and any therapeutic review that the GP might wish to carry out. Solvay, therefore, had no involvement whatsoever in any protocol followed by the GP in making management decisions for his patients. It was clear, nevertheless, from the agreement and the template letters that Solvay understood that the GP intended to call back patients before reviewing their management or making any decisions on treatment.

PANEL RULING

The Panel considered that it was not necessarily unacceptable for pharmaceutical companies to sponsor audits in general practice. The supplementary information to Clause 18.4, Switch and Therapy Review Programmes, stated that switch programmes, whereby pharmaceutical companies paid for, or facilitated, patients' medicine being simply changed from medicine A to medicine B were prohibited under the Code. Such arrangements would be seen as companies in effect paying for prescriptions. Genuine therapeutic reviews, however, which aimed to ensure that patients received optimal treatment following clinical assessment were a legitimate activity for a pharmaceutical company to support and/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's treatment must be documented with evidence that it was made on rational grounds.

The Panel considered that irrespective of a company's degree of involvement and whether the independent service provider, such as an audit nurse, was appointed by the pharmaceutical company or directly by the service recipient the pharmaceutical company should still be able to demonstrate that any medical and educational goods and services which it provided or facilitated complied with Clause 18.4 and its supplementary information. The parties' roles and responsibilities should be abundantly clear and records kept.

The Panel noted that the letters from Solvay to the GP in question referred to supporting '… your audit of your patients with cardiovascular risk factors'. This was inconsistent with its description of its service (in the penultimate paragraph of its response) as an audit to identify patients with various cardiovascular risk factors. The letter from Solvay to the complainant referred to supporting '… a practice audit to identify patients with cardiovascular disease who may not have been on optimal medical treatment'. The letter from Solvay to the Authority referred to 'a patient identification programme'. The Field Force Working Guidance referred to both. Solvay submitted that it had given the GP four unconditional grants for help to audit patients at increased cardiovascular risk to review their therapy between November 2006 and June 2007. In all, the doctor had been given approximately £1,700 which was to cover the cost of a nurse to do the audit. The letters to the GP further noted that Solvay understood that 'following the audit the practice will carry out a therapeutic review of the patients and decide on appropriate continued management of the patients so identified'. The Panel noted Solvay's initial submission that its Field Force Working Guidance and the signed letter of agreement with the GP required that patients identified during the audit would be subsequently reviewed by the GP for any appropriate clinical decisions. In response to a request for further information, however, Solvay drew a distinction between the audit and any therapeutic review which the GP might subsequently wish to carry out. The Panel noted that as part of the agreement the GP was offered generic template letters to recall patients for review.

The Panel considered that the letter to patients provided by the practice was unacceptable as far as the Code was concerned. However the letter provided bore no resemblance to the templates included in the Solvay Field Force Working Guidance. The Panel considered that it was not clear whether patients prescribed Omacor following the audit met the licensed indications or not although, from the information provided, it appeared that at least some of them would have done.

The Panel disagreed with Solvay's description of the grant as 'unconditional'; the money had been granted for the specific (conditional) purpose of supporting an audit of patients with cardiovascular risk factors. The Panel noted that the details of that audit were unknown to Solvay. It appeared that the company had no way of knowing if it was paying for a clinically robust audit or not. This was unacceptable. In the Panel's view, pharmaceutical companies sponsoring third parties, particularly individuals, must be reasonably confident that their proposed activities were clinically sound and complied with the Code. In addition to funding and agreeing that the audit be performed by an external healthcare practitioner, Solvay had, in each of the four letters to the doctor, stated that the audit would be performed by a named nurse. Solvay had, in effect, provided the nurse to do the audit who the company understood had some expertise in similar audits. Again the Panel considered that this was unacceptable; if the company was recommending staff to carry out the audit it should be sure that they had the necessary expertise. In the Panel's view, by introducing the nurse to the practice, Solvay had to assume some responsibility for her actions.

With regard to the provision of nursing staff the Panel was concerned to note that Solvay had initially named two individuals but had later stated that this was an error in that one of those named was understood to be a practice manager. Nonetheless the final letter from Solvay to the GP (13 June) had the nurse's name crossed out and the assumed practice manager's name written in by hand. There was no information as to who had changed the letter or who had conducted the final audit.

Field Force Working Guidance (SOP SHL C33) issued by Solvay gave guidance on the provision of unconditional medical grants for audit of care in patients in general practice. The guidance stated that if asked for financial assistance with a patient identification audit in the relevant therapeutic area eg coronary heart disease/cardiovascular disease that might encompass patients who had had a previous myocardial infarction, hypertension, lipid abnormalities and stroke, representatives could tell health professionals that Solvay was able to offer help. The guidance, however, did not refer to the company reviewing the proposed audit protocol so as to ensure that it was supporting a valid audit. The guidance also noted that Solvay could provide an external agent to perform the audit and, if requested, template letters that the surgery could use in order to recall patients to review their therapy.

The Panel was concerned about the representative's role in the audit at issue. Although Solvay stated that the representative had sought authority for financial support to be given, it appeared that no regional sales manager or healthcare development manager had discussed the project with the GP as recommended in the Field Force Working Guidance. The representative had provided the GP with the contact details of a nurse who would conduct the audit and had arranged for the GP to sign the agreement regarding the support to be provided by Solvay. The representative had delivered the cheque which represented the fee to be paid to the nurse for conducting the audit. In the Panel's view the delivery of cheques to doctors by representatives in this way gave a very poor impression; it might be perceived by some to be an inducement to prescribe the company's products given the prime role of a representative was to promote medicines.

The Panel noted Solvay's involvement with the audit and subsequent therapy review and considered that it was inextricably linked to it. The company had given the GP approximately £1,700 but had had no oversight of the protocol; it had, in effect, provided a nurse to do the audit although it appeared to have no evidence that she was suitably experienced to be able to conduct the audit or knowledge of what she was going to do. The Panel considered that the vague arrangements which existed were wholly unacceptable; the arrangements were such that Solvay had no way of ensuring that the grant which it had given to the GP would be used for an appropriate purpose. The Panel considered that the arrangements were such that they did not constitute a bona fide medical and educational good and service. The Panel ruled a breach of Clause 18.4 of the Code.

The Panel noted that data provided by the complainant showed that the prescribing of Omacor in the practice in question greatly exceeded the two highest Omacor prescribing practices in the local PCT and that the other 60 or so practices in the area prescribed almost negligible amounts of this medicine. The Panel further noted that shortly after receiving each letter from Solvay regarding the provision of more money (November 2006, January, April and June 2007) prescribing of Omacor in the practice in question increased. The Panel also noted the complainant stated that following the meeting with the representative the doctor considered his patients would benefit from Omacor and he signed an agreement with Solvay. The Panel noted its concerns about the role of the representative and the delivery of cheques to the doctor by the representative. The Panel considered that on the balance of probabilities such payment by a representative in association with an unacceptable service amounted to an inducement to prescribe Omacor in breach of Clause 18.1. The Panel had no evidence that the grants constituted the disguised promotion of Omacor. No breach of Clause 10.1 was ruled.

The Panel was very concerned about the overall arrangements set out above. The Panel further considered that given its involvement in the process, Solvay's failure to assume any responsibility for the audit which it facilitated meant that the conduct of employees had fallen short of competent care such as to bring discredit upon or

reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned that Solvay appeared to have no procedures in place for ensuring that grants given to facilitate general practice audit were spent on valid audits/therapy reviews and the like. The Panel was also concerned that Solvay would recommend third parties to perform the audits/reviews, without knowing their relevant qualifications or experience to perform such tasks, but take no responsibility for their actions. The Panel decided to report Solvay to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. In accordance with Paragraph 7.1 of the Constitution and Procedure, the Panel further required Solvay to suspend the provision of grants for patient identification programmes and the like such that no new agreements were signed.

COMMENTS FROM SOLVAY ON THE REPORT

Solvay stated that it had reflected very carefully on the Panel's findings. It had investigated the matter thoroughly and examined its policies and practices relating to similar programmes. The company took its responsibilities as a pharmaceutical company very seriously and always sought to comply with the Code. The company regretted very much that this case had arisen and had led to the Panel ruling that a programme intended to benefit patients and the NHS did not comply with the Code.

Solvay submitted that the patient identification programmes which it sponsored were conceived and, so far as it understood, were executed as audits, stopping short of a consultation and any clinical decision making. Such an audit was essentially a snapshot recording an existing state of affairs rather than an analysis of what should be happening. An audit was an essential preliminary to a therapy review and, of its nature, was an activity which benefitted patients and the NHS. Once the GP had the information from the audit he could decide how to use it. A therapy review would be an obvious second step, but the value in the audit was in the extraction of information which might be used for planning, appraisal and public health purposes, quite apart from its use in the initiation of individual changes of therapy.

Many companies, including Solvay, had sponsored audits, but did not wish or think that it was proper to become involved in a doctor's clinical decision making or prescribing because their own products might feature in those decisions. Solvay designed the patient identification programmes in good faith and with the best of intentions to try to provide the sort of useful audit service which it believed would benefit the NHS and patients. The company had considered that such audits were less likely to give rise to concerns under the Code because they stopped short of becoming involved with therapeutic decisions or protocols, the full responsibility for which remained, as Solvay thought proper, with the GP. Solvay's reading of the Code and previous cases had supported it in this belief.

Following receipt of the Panel's rulings Solvay was carrying out a thorough and urgent review of all of its procedures to ensure that the very important lessons derived from the ruling were learnt and put into practice by all staff. Solvay noted, however, that some of the most concerning aspects that had emerged – such as the letter sent to patients and the quality of the GP's subsequent prescribing decisions – occurred after the completion of the company sponsored audit and were matters over which Solvay had no control.

Solvay stated that the points it made in mitigation did not qualify its respect and support for the Authority and its acceptance of the Panel's rulings. The company repeated that it regretted the matter had come before the PMCPA and its ongoing commitment to compliance with the Code.

At the consideration of the report Solvay's representatives stated that Solvay had not intended to offer any inducement to prescribe Omacor, it considered the payments to be unconditional grants. The representatives apologised for being found in breach of the Code.

The representatives stated that the patient identification programme at issue had ceased in February 2009. Since then a review of the company's standard operating procedures and a further training programme for staff involved in Code issues had been commissioned. The revised standard operating procedures were due to be completed by May 2009 and staff training by June 2009. External Code consultants had been employed.

In addition all sales staff and head office staff involved with the Code had been trained on the Code in December 2008.

APPEAL BOARD CONSIDERATION

The Appeal Board was very concerned that Solvay had provided grants in the form of cheques via its representative to the GP on four separate occasions. The Appeal Board considered that it was inappropriate for a representative to hand over money to a doctor. The company had no processes to enable it to check that the money was used to pay a nurse to conduct an audit and how long that would take or that the audit itself was appropriate. Further there was no assessment of the first audit before providing a cheque to the same doctor for the next audit. The Appeal Board did not accept that the payment to the doctor was unconditional as submitted by Solvay. It was provided for a specific reason – ie an audit. The Appeal Board was further concerned that the nurse, introduced to the GP by Solvay and employed by him to undertake the patient identification programme, had not been assessed by the company with regard to her ability to carry out the task for which she was to be paid. There was a failure of management.

The Appeal Board further noted that there appeared to be a marked consequential increase in the prescribing of Omacor by the GP concerned and it queried whether, as a result, patients had been put at risk.

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

APPEAL BOARD FURTHER CONSIDERATION

The audit was conducted in June 2009. The Appeal Board was concerned to note that the audit report demonstrated that Solvay had clearly lacked processes to ensure compliance with the Code. Further policy changes were still required. The Appeal Board thus decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require a further audit of Solvay's procedures in relation to the Code to be carried out by the Authority in November when it expected Solvay's standard operating procedures (SOPs) to be completed. On receipt of that audit report the Appeal Board would consider whether further sanctions were necessary.

In accordance with Paragraph 13.6 of the Constitution and Procedure the Appeal Board decided that an interim case report should be published on the PMCPA website.

Upon receipt of the report of the November 2009 re audit the Appeal Board noted that Solvay had made much improvement since the audit in June 2009. The Appeal Board decided that on the basis that the recommendations from the re audit were either implemented or ongoing no further action was required.

Complaint received	**14 January 2009**
Undertaking received	**10 March 2009**
Appeal Board consideration	**23 April 2009**
Interim case report published	**1 June 2009**
Appeal Board consideration	**23 July 2009**
Case completed	**9 December 2009**

CASE AUTH/2258/8/09

ANONYMOUS v SANOFI-AVENTIS

Conduct of representatives

An anonymous uncontactable complainant alleged that Sanofi-Aventis oncology representatives in one UK region had demanded regional data on patient numbers being treated on docetaxel (Sanofi-Aventis' product Taxotere) and its competitor medicines for all local hospitals. Printouts of this data comparing 2008 and 2009 had been supplied; the complainant asked that this practice be stopped immediately. Separately, this had led to adverse event patient information for named patients being emailed to representatives in breach of patient confidentiality and adverse event reporting procedures. The complainant questioned whether Sanofi-Aventis had followed the appropriate adverse event reporting procedures.

The detailed response from Sanofi-Aventis is given below.

The Panel noted that the parties' accounts differed. The complainant had not submitted any evidence in support of their allegation. The complainant had to establish his/her case on the balance of probabilities.

The Panel noted Sanofi-Aventis' submission regarding arrangements for the promotion of docetaxel by its sales force and the purchase of sales data. Representatives were expected to identify customer usage of Taxotere in specific tumour types. They had not been instructed to demand such data and no briefings had been issued. The Panel considered that there was no evidence to support the allegation that representatives had demanded data on patient numbers as alleged. No breach of the Code was ruled.

In relation to the alleged receipt of named patient data the Panel noted that an email from a hospital pharmacist to a representative about adverse reactions to Taxotere named the patients involved; the representative subsequently forwarded the email to her line manager and two colleagues. Patient details had not been requested by the representative or by the company on the Drug Experience Report Form. There was no evidence that the representative had requested patient details as inferred by the complainant. However the Panel was very concerned that the representative had subsequently forwarded the email to two other representatives. Once the representative knew that she ought not to have named patient data and that the onward transmission of such data was unacceptable she immediately notified the other representatives not to open the email. The Panel considered that the representative's original decision to circulate the email containing named patient data to anyone other than the pharmacovigilance department was unacceptable such that she had failed to maintain a high standard of ethical conduct in the discharge of her duties. A breach of the Code was ruled. This ruling was accepted. High standards had not been maintained; a breach of the Code was ruled. Upon appeal by Sanofi-Aventis, the Appeal Board noted that the company had accepted the ruling of a breach of the Code with regard to the representative's onward transmission of confidential patient data. The representative's manager, however, quickly spotted the mistake and the representative took immediate steps to rectify her error. In that regard the Appeal Board did not consider that high standards had not been maintained and no breach of the Code was ruled. The appeal on this point was successful.

The Panel noted that a presentation for new starters 'The Handling of Adverse Drug Reactions' explained the importance of pharmacovigilance and reporting procedures. Refresher training gave more details. Representatives were instructed to provide details of *inter alia* 'Patient details (initials, age, age range, gender). A slide headed 'Good Reporting Practice' referred to patient's demography (mostly age); medical history/concomitant diseases and additional information. Neither presentation referred to the importance of maintaining patient confidentiality which the Panel considered was a significant omission such that the material in effect advocated a course of action which was likely to lead to a breach of the Code, a breach of the Code was ruled. Upon appeal by Sanofi-Aventis, the Appeal Board noted that neither presentation referred to the importance of maintaining patient confidentiality. This was an important omission; there should have been some reference to anonymised data. Nonetheless, the Appeal Board did not consider that such an omission positively advocated a course of action which was likely to lead to a breach of the Code. No breach of the Code was ruled. The appeal on this point was successful.

The representative had reported information on side effects to the company's scientific service; no breach of the Code was ruled.

The Panel was concerned about the conduct of the representative but noted its rulings above. Overall the Panel did not consider that the representative's conduct warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

An anonymous uncontactable complainant complained about the conduct of Sanofi-Aventis oncology representatives.

COMPLAINT

The complainant alleged that Sanofi-Aventis oncology representatives in one UK region had demanded data on patient numbers being treated on docetaxel (Sanofi-Aventis' product Taxotere) and its competitor medicines for all local hospitals. Printouts of this data comparing 2008 and 2009 had been given to them; the complainant asked that this practice be stopped immediately. Separately, this had led to adverse event patient information for named patients being emailed to representatives in breach of patient confidentiality and adverse event reporting procedures. The complainant questioned whether Sanofi-Aventis had followed the appropriate adverse event reporting procedures.

When writing to Sanofi-Aventis the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 15.6, 15.9 and 18.4 of the Code.

RESPONSE

Sanofi-Aventis submitted that it had conducted an extensive investigation into the activities of all oncology representatives in question. The investigation had included reviews of all representatives' emails and documents saved on company systems and interviews with those representatives who were most relevant to the findings. The complainant referred to data comparing 2008 and 2009 usage figures being provided to representatives; there was otherwise no clear time frame for the activities subject to complaint and, on this basis, Sanofi-Aventis had therefore concentrated its investigation on the 6 months period prior to the complaint.

Sanofi-Aventis noted that the complainant alleged that Sanofi-Aventis representatives had demanded data on patient numbers being treated on docetaxel and its competitor medicines for all hospitals within one region. Printouts of this data comparing 2008 and 2009 had been given to them and the complainant had asked that this practice be stopped immediately. Docetaxel (Taxotere) was licensed in several different tumour types but it was only actively promoted for use in breast and prostate tumours, by representatives dedicated to one or the other type. Thus, each hospital would have two Taxotere representatives, one promoting its use in breast and one in prostate. However sales data did not detail Taxotere usage according to tumour type; it simply reported total sales for any given hospital. Such data were inadequate for detailed planning and reporting purposes for individual tumour-specific representatives. In order to redress this:

- The company purchased data from the NHS which showed the breakdown by tumour type of Taxotere and its competitors, for the local area. The NHS sold this data to a wide range of companies and there was considerable uptake of the report by the pharmaceutical industry. These were the only data received by the company from the NHS which included any information on competitors. A copy of the most recent data was provided.

- Representatives were expected, in the normal course of their duties, to identify customer usage of Taxotere in specific tumour types. This was a standard part of their duties and consistent with maintaining good relations with NHS customers and appropriate planning of current and future representative activity. However, representatives were neither incentivised for obtaining such data, nor penalised for not. On this basis, there had been no formal written or verbal briefings issued on the matter. Sanofi-Aventis had conducted a thorough review of all briefing documents, none of which directed, or could be interpreted to direct, sales representatives to 'demand' usage data. It was clear that these data belonged to the NHS, and it was the goodwill of individual health professionals which enabled Sanofi-Aventis to receive this feedback; while there had never been any instruction to 'demand' such data, to do so would, in any case, be counter-productive and severely detrimental to the relationship between health professional and representative.

Although availability of such data helped the company to evaluate whether sales objectives or specific goals had been achieved, Sanofi-Aventis confirmed that collection of such data was not a specific objective for representatives.

Sanofi-Aventis was confident that its representatives maintained professional relations with all customers and it had found no evidence of any 'demands' for any data relating to product usage, either for Taxotere or competitor products. Sanofi-Aventis therefore denied any breaches of the Code as alleged by the complainant in this context.

Sanofi-Aventis attached the utmost importance to the correct and timely reporting of all suspected adverse events relating to its medicines. On this basis, all staff, including representatives, were trained in adverse event reporting requirements and related company procedures on first joining the company, and periodically thereafter. Copies of the training materials used for new staff and for refresher training of representatives were provided, as were the company's standard operating procedures for pharmacovigilance training and reporting of suspected adverse events. The requirement to report all adverse events was also included in the training on the Code given to all representatives joining the company, a copy of which was also provided.

Sanofi-Aventis noted that the complainant had also alleged that adverse event patient information for named patients had been emailed to representatives in breach of patient confidentiality and adverse event reporting procedures. As the complainant had linked this part of the complaint to the first which related to a specific UK region, Sanofi-Aventis submitted that it had again investigated this in relation to the oncology

representatives who worked in this region, over the same time period as above, ie the 6 months prior to the complaint. Again, Sanofi-Aventis had reviewed all emails and documents for each in order to identify material relevant to the complaint. Additionally, Sanofi-Aventis had reviewed all adverse event reports made via its oncology sales team nationwide over the last 12 months for any patient names or other uniquely identifying details.

Sanofi-Aventis submitted that it had identified a single incident in which a representative received patient names as part of the follow up of an adverse event report.

The representative in question visited a hospital on 15 June 2009 and was informed of several hypersensitivity reactions to Taxotere by the chemotherapy nurses. In accordance with company procedures, the representative notified the pharmacovigilance department within one working day, ie on 16 June. The same day, the pharmacovigilance department sent adverse event reporting forms to the representative for distribution to the relevant staff at the hospital. The pharmacovigilance department subsequently submitted an initial report as required by company procedures, on 19 June. Unfortunately, no follow-up information was received from the hospital and so the pharmacovigilance department asked the representative to visit the hospital again to obtain the required information. As a result, a pharmacist at the hospital subsequently emailed the representative with details of the reactions experienced, including patient names in full. At no stage had names been requested, either directly by the representative or via the Drug Experience Report Form used for adverse event reporting (an example of which was provided). The representative forwarded this email to her manager and two colleagues in the area for information; her manager responded the next day informing her that she must not be in possession of patient names as this could compromise her position and had implications for patient confidentiality (the email trail was provided). The representative subsequently:

- contacted the pharmacist at the hospital to thank her for her cooperation, but pointed out that as a representative she should not be privy to patient names and that they had been deleted;
- attempted (twice) to recall the emails with patient details which she had forwarded to colleagues; when this failed she sent a message asking that the email from the hospital pharmacist not be read;
- reported the follow-up information (with patient names deleted) to the pharmacovigilance department.

In summary, Sanofi-Aventis submitted that its extensive investigations had identified only one incident where patient names had been provided, entirely unsolicited, to an oncology representative by a hospital pharmacist. It was regrettable that the representative did not delete the patients' names from the information she sent on to her manager and two close colleagues working in the same area. However this oversight was immediately identified by her manager and the representative then took all measures available to her to mitigate the effects of her actions. Sanofi-Aventis maintained detailed systems and training on adverse event reporting for all staff including representatives, and in relation to this case, reporting requirements were adhered to as far as was possible, with the exception of the transmission of patient names. Sanofi-Aventis therefore denied any suggestions that this was anything other than an isolated incident and refuted the alleged breaches of the Code.

Sanofi-Aventis submitted that the complainant's allegations had been addressed in detail above. Whilst Sanofi-Aventis had conducted an extensive investigation into the issues involved, it noted that the complainant had not provided any evidence to substantiate his/her assertions. Overall, Sanofi-Aventis submitted that Clause 18.4 was not relevant to the circumstances and there was no evidence to indicate any breach of Clauses 2, 9.1, 15.2, 15.6 and 15.9.

PANEL RULING

The Panel noted that the parties' accounts differed. Sanofi-Aventis denied the complainant's allegation that representatives had demanded data on the number of patients treated with docetaxel. The complainant who was anonymous and non contactable had not submitted any evidence in support of their allegation. The complainant had to establish his/her case on the balance of probabilities.

The Panel noted Sanofi-Aventis' submission regarding arrangements for the promotion of docetaxel by its sales force and the purchase of sales data. Representatives were expected to identify customer usage of Taxotere in specific tumour types. There had been no instruction to demand such data and thus no verbal or written briefings had been issued on this point. The Panel considered that there was no evidence to support the allegation that representatives had demanded data on patient numbers as alleged. No breach of Clauses 15.2 and 15.9 was ruled.

In relation to the alleged receipt of named patient data the Panel noted that a representative had initially been told of several hypersensitivity reactions to Taxotere by hospital nurses. This was followed up by the representative and the pharmacovigilance department at Sanofi-Aventis. The Panel noted that an email from a hospital pharmacist to the representative about these adverse events named the patients involved; the representative subsequently forwarded the email **to** her line manager and two colleagues. Patient details had not been requested by the

representative or by the company on the Drug Experience Report Form. The Panel noted that the representative had legitimately followed up the initial report of the adverse events. There was no evidence that the representative had requested patient details as inferred by the complainant. However the Panel was very concerned that the representative had subsequently forwarded the email to two other representatives. Once the representative was made aware that she ought not to be in possession of named patient data and that the onward transmission of such data was unacceptable she immediately took steps to notify the other representatives not to open the email. The Panel considered that the representative's original decision to circulate the email containing named patient data to anyone other than the pharmacovigilance department was unacceptable such that she had failed to maintain a high standard of ethical conduct in the discharge of her duties. A breach of Clause 15.2 was ruled. This ruling was accepted. High standards had not been maintained; a breach of Clause 9.1 was ruled. This ruling was appealed.

The Panel noted that the presentation for new starters 'The Handling of Adverse Drug Reactions' explained the importance of pharmacovigilance and reporting procedures. The refresher training gave more details. Representatives were instructed to provide details of *inter alia* 'Patient details (initials, age, age range, gender). A slide headed 'Good Reporting Practice' referred to patient's demography (mostly age); medical history/concomitant diseases and additional information. Neither presentation referred to the importance of maintaining patient confidentiality which the Panel considered was a significant omission such that the material in effect advocated a course of action which was likely to lead to a breach of the Code, a breach of Clause 15.9 was ruled. This ruling was appealed.

The representative had reported information on side effects to the company's scientific service as required by Clause 15.6 so no breach of that clause was ruled.

The Panel was concerned about the conduct of the representative but noted its rulings above. Overall the Panel did not consider that the representative's conduct warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure. No breach of Clause 2 was ruled.

The Panel made no ruling in relation to Clause 18.4 as on receipt of the company's response it transpired that it was not relevant to the matters at issue.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis submitted that its pharmacovigilance training material for representatives incorporated the requirements outlined in guidance issued by the Medicines and Healthcare products Regulatory Agency (MHRA) with regard to patient details required to be reported where there was a suspected adverse event. The training materials did not extend beyond these requirements. In particular, neither the materials nor the company advocated or suggested the collection or dissemination of patient names or other details which would compromise patient confidentiality. This was borne out by the evidence that, apart from the one incident on which this case was based, a comprehensive review of all adverse event reports showed that patient names were never used or referred to, and all patient details were within the MHRA guidance on which Sanofi-Aventis's training was based. In the one case where patient names were transmitted within the company by a representative, the names were not requested or solicited by the representative and following her manager's intervention, she contacted the reporting pharmacist to clarify the requirements in this area (audit trail previously submitted).

For the avoidance of doubt, Sanofi-Aventis would include statements to this effect in all future training materials. However, the current training materials were appropriate; they included correct and appropriate instructions on what patient data to collect, and although further detail on patient confidentiality was not formally presented, the otherwise universal adherence of representatives to these requirements did not support the notion that the materials advocated a course of action likely to lead to a breach of the Code. Sanofi-Aventis therefore appealed against the ruling of breach of Clause 15.9, ie that on the balance of probabilities, the training advocated a course of action which would be likely to breach the Code.

Sanofi-Aventis appealed the Panel's ruling of breach of Clause 9.1 because it had appealed the ruling of breach of Clause 15.9 and because its extensive investigation into the matters raised by the complainant had revealed one isolated incident of inappropriate transmission of patient names (which were unsolicited by Sanofi-Aventis representative), and otherwise no evidence of any more widespread or systematic divergence from the MHRA requirements on patient details. Given this unique event, which was not the result of any company instruction, Sanofi-Aventis submitted that it was not possible to determine, on the balance of probabilities, that it had failed to meet high standards overall.

APPEAL BOARD RULING

The Appeal Board noted that Sanofi-Aventis had accepted the ruling of a breach of Clause 15.2 with regard to the representative's onward transmission of confidential patient data to her field force colleagues. The representative's manager, however, quickly spotted the mistake and the representative took immediate steps to rectify her error. In that regard the Appeal Board did not consider that high standards had not been

maintained and no breach of Clause 9.1 was ruled. The appeal on this point was successful.

The Appeal Board noted that neither the presentation for new starters, 'The Handling of Adverse Drug Reactions', nor the refresher training slides referred to the importance of maintaining patient confidentiality. The Appeal Board thought that this was an important omission; there should have been some reference to anonymised data. Nonetheless, the Appeal Board did not consider that such an omission positively advocated a course of action which was likely to lead to a breach of the Code. No breach of Clause 15.9 was ruled. The appeal on this point was successful.

Complaint received **24 August 2009**

Case completed **11 November 2009**

CASE AUTH/2259/8/09

JOHNSON & JOHNSON/DIRECTOR v PFIZER

Promotion of Champix

Johnson & Johnson complained about the promotion of Champix (varenicline) by Pfizer. The items at issue were a leavepiece and an advertisement published in GP. As the complaint involved an alleged breach of undertaking that element was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

The detailed response from Pfizer is given below.

The leavepiece was entitled 'How you and 12 weeks of Champix can aid smoking cessation with your patients'. Johnson & Johnson alleged a breach of the undertaking given in Case AUTH/2203/1/09.

In the leavepiece now at issue, a full page was dedicated to a comparison between Champix and NRT. The page was headed 'Prescribe 12 weeks of Champix for your motivated quitters' and included a bar chart seemingly comparing Champix and NRT at 12 weeks. Below the bar chart were a number of claims relating to the comparison. Johnson & Johnson was concerned about the presentation data from Aubin *et al*.

Johnson & Johnson alleged that although the footnote provided further details about the study, including study design, patient numbers, study duration and primary and secondary endpoints, it was not enough. The Panel's ruling in Case AUTH/2203/1/09 made it clear that any necessary additional information about the study should be included in the body of the advertisement. Providing further information only by way of a footnote was not consistent with the previous Panel ruling.

Johnson & Johnson also alleged that a major issue with Aubin *et al* was that previous treatment might have influenced patient motivation – it was well known that motivation played a role in the success of quit attempts. The importance of previous treatment was particularly relevant in the context of an open-label study where the subjects would have known which treatment they were receiving. It was highly likely that any such bias would favour the new treatment (Champix) as it would be viewed by subjects, and perhaps investigators, as 'novel' and, possibly, an 'advance' in smoking cessation. That Champix was a prescription only medicine and NRT had been available over the counter for many years might also have been significant. An exclusion for patients who had used NRT within the previous 6 months was not rigorous enough to ensure that previous NRT treatment did not bias the result in favour of Champix.

Johnson & Johnson alleged that this potential difference in motivation between the groups was demonstrated by the fact that 2% of patients randomised to NRT dropped out of the study compared with 0.5% randomised to Champix. This was acknowledged by the authors who stated 'A limitation of this study was the open-label design. The differential dropout rate after medication assignment and before the first dose of treatment suggests that some motivational bias may have influenced the results'.

Despite the Panel's ruling that sufficient information relating to the nature of the Aubin data should be included in promotional material, Johnson & Johnson noted that there was no reference to the fact that almost 50% of participants had already received NRT and the potential impact of this upon the results. Therefore, not all relevant information had been presented. Moreover, the footnote on the summary page headed '12 weeks of Champix with quit support helps smokers break their addiction' contained even less information about the study. In particular, there was no mention of its open-label nature.

In summary, Johnson & Johnson alleged that Pfizer's use of a footnote to provide further information about Aubin *et al* was inconsistent with the Panel's ruling which suggested that it should be included as part of the main body of the advertisement. In addition, inadequate information had been provided to explain the failings of the study particularly with regard to previous treatment and ultimately motivation. Finally, Johnson & Johnson was concerned that the leavepiece summary page provided only very limited information about the study and did not clarify that it was open-label.

Johnson & Johnson thus alleged that Pfizer had not complied with the undertaking given in Case AUTH/2203/1/09. In addition, the material was misleading and did not enable the recipient to form their own opinion of the therapeutic value of the medicine.

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

The first page at issue in the leavepiece (the inside central page) was headed 'Prescribe 12 weeks of Champix for your motivated quitters [5]*' beneath which was a bar chart which compared the

continuous abstinence rate in the last 4 weeks of treatment of Champix (55.9%) with that of an NRT patch (43.2%) at 12 weeks. The bar chart was headed 'Champix vs. NRT patch at 12 weeks (NiQuitin CQ Clear) (N=746) [5]*'. Three bullet points followed beneath the bar chart including: 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' and 'At 1 year, the quit rate was 26.1% for Champix vs. 20.3% for NRT patch (p=0.056, not significant)'. All the data was referenced to Aubin *et al*. The asterisk by the two claims took readers to a footnote at the bottom of the page, 'Aubin H-J *et al*. An open label, randomised, multi-centre clinical trial of 746 smokers directly compared the recommended treatment courses of Champix for 12 weeks with the NRT patch (NiQuitin CQ Clear) for 10 weeks. The primary endpoint was the continuous abstinence rate (CO [carbon monoxide]-confirmed) at weeks 9-12 for Champix and at weeks 8-11 for NRT. A secondary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-52 for Champix and at weeks 8-52 for NRT'.

Less information about Aubin *et al* appeared on the summary page which was headed '12 weeks of Champix with quit support helps smokers break their addiction' and featured 3 bullet points including the claim 'Significantly higher quit rate at 12 weeks versus NRT patch* (NiQuitin CQ Clear), bupropion and placebo[4, 5]'. The comparison with NRT patch was referenced to Aubin *et al* and that with bupropion and placebo was referenced to Nides *et al* (2008). Two footnotes gave limited details about each study; that for Aubin *et al* described its primary and one secondary endpoint, continuous abstinence rate.**

The Panel noted that in the previous case, Case AUTH/2203/1/09, a journal advertisement with the claim 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' was ruled in breach of the Code. The substantiating data was Aubin *et al*, limited details of which appeared as a footnote to a separate claim. The footnote explained that the recommended treatment course for Champix was 12 weeks and for NRT patch (NiQuitin CQ Clear) was 10 weeks. Continuous abstinence rate was CO-confirmed at weeks 9-12 for Champix and at weeks 8-11 for NRT. No further details about Aubin *et al* appeared in the advertisement.

In the present case, Case AUTH/2259/8/09, the Panel noted that there were differences between the claim at issue previously 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' and the two pages in the leavepiece now at issue. The claim at issue previously was not reproduced in the leavepiece although, in the Panel's view the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was closely similar. The issue was whether sufficient details about Aubin *et al* had been given such that the leavepiece was not caught by the undertaking previously given. The Panel noted that the only details about the study design for Aubin *et al* appeared in footnotes. The footnote on the inside central page mentioned the open-label design, that on the summary page did not. The Panel noted that claims in promotional material should be capable of standing alone as regards the requirements of the Code. Information integral to a reader's understanding of a claim should not be relegated to a footnote, it should appear in the immediate visual field of the claim itself. The open-label nature of the study was a very relevant factor for readers in assessing the claims at issue in both cases. The Panel noted that whilst changes had been made to the material these were insufficient to address the concerns raised by the Panel previously. Whilst it was of course not necessary to detail every aspect of the study, sufficient information should be given such that the reader was aware of the basis of the data. Pertinent information about Aubin *et al* was not an integral part of the main body of the pages at issue in the leavepiece. The footnotes were insufficient in this regard. The leavepiece was thus caught by the undertaking previously given. A breach of the Code was ruled. High standards had not been maintained and the material brought discredit upon and reduced confidence in the pharmaceutical industry; breaches of the Code, including of Clause 2, were ruled.

The Panel noted its comment above about the use of footnotes. Overall, the Panel considered that insufficient information had been provided to enable a reader to form their own opinion of the therapeutic value of the medicine as alleged. A breach of the Code was ruled.

Johnson & Johnson alleged that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was misleading and all-encompassing. The claim was referenced to Aubin *et al* wherein Champix was compared to the NiQuitin CQ Clear patch (manufactured by GlaxoSmithKline). The NiQuitin CQ Clear patch was a specific formulation which differed from other patches in terms of its release characteristics and pharmacokinetic profile. Johnson & Johnson alleged that the claim implied that all NRT patches were the same and that Champix had proven superiority over all patches. This was not so. There was no clinical efficacy data directly comparing Nicorette patch with any other NRT patch. In addition, Johnson & Johnson was unaware of any direct comparisons between Champix and any nicotine patch other than NiQuitin CQ Clear. Therefore, to imply that Champix was more effective than all NRT patches was misleading and disparaged other NRT patches including Nicorette.

Johnson & Johnson alleged that Pfizer had not taken into account differences between NRT patches and the leavepiece was therefore misleading and the information presented was not accurate, balanced, fair and unambiguous.

The Panel noted that the only references to NiQuitin CQ Clear were in the heading to the bar chart and once in the footnote at the bottom of the page. All other references on the page, including other labelling on the bar chart, were to 'NRT patch'. The Panel did not accept Pfizer's submission that it followed that after the first substantive mention of the comparator treatment all future references to 'NRT patch' would, in effect, mean NiQuitin CQ Clear. That was not necessarily so. The relevant bar of the bar chart was labelled 'NRT patch'. Further, given that no information about the study design appeared in the body of the page, a reader might assume there was more than one arm of the study and thus more than one NRT comparator. The position was not clear.

The Panel noted Johnson & Johnson's submission that there was no direct comparative efficacy data between Nicorette and any other NRT patch and that the NiQuitin CQ Clear patch differed from other patches in terms of its release characteristics and pharmacokinetic profile. Overall, the Panel considered that in the context in which it appeared the claim at issue could not take the benefit of the reference to NiQuitin CQ Clear in the title of the bar chart as submitted by Pfizer. Claims had to be able to stand alone under the Code. The Panel considered that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was misleading as alleged. A breach of the Code was ruled.

Johnson & Johnson noted that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' related to differences in treatment timing between NiQuitin CQ Clear and Champix. Johnson & Johnson alleged that readers should have been made aware of this. In Aubin *et al*, the primary endpoint was continuous abstinence rates for Champix at weeks 9-12 and for NiQuitin CQ at weeks 8-11. Treatment duration in the Champix group was 12 weeks, compared with 10 weeks for the NRT group. These differences in treatment duration and measurement of the primary endpoint introduced a potential source of bias. Johnson & Johnson alleged that the claim clearly stated 'Champix vs NRT patch at 12 weeks …' which was therefore incorrect. The heading of the graph immediately above the claim also inaccurately stated '12 weeks'. Given this, both the claim and the title of the bar chart were inaccurate and inconsistent with Aubin *et al* and the footnote.

The Panel noted that the treatment periods of both NiQuitin CQ Clear and Champix in Aubin *et al* reflected that recommended in their summaries of product characteristics (SPCs). The Panel noted that the 12 week treatment period for Champix was referred to in the prominent page heading 'Prescribe 12 weeks of Champix for your motivated quitters', again in the title of the bar chart and in the first bullet point. A reference also appeared in the footnote. Comparable information for NiQuitin CQ Clear was not given in the main body of the page. The Panel noted its comments about footnotes above. Whilst the footnote made it clear, *inter alia*, that Aubin *et al* examined NiQuitin CQ Clear for its recommended treatment period of 10 weeks and made clear the differences in the measurement of the primary endpoint the Panel considered that the relegation of this information to a footnote meant that overall the page gave a misleading impression of the treatment duration and measurement of the primary endpoint for NiQuitin CQ. A breach of the Code was ruled.

Beneath the heading 'Champix and the NHS stop smoking service' appeared a highlighted box featuring 3 pie charts headed 'Successful quitters at week 4 follow-up by treatment used (April 2007 – March 2008)'. The pie charts depicted separately the percentage of successful quitters for Champix (63%, n=97,259); NRT (49%, n=474,311) and bupropion (53%, n=22,348). The heading was asterisked to a footnote at the bottom of the page which read 'Based on a statistical report presenting final results from the monitoring of the NHS Stop Smoking Service from the period April 2007 – March 2008. Successfully quit = not smoking at the 4 week follow up (self-reported, not necessarily CO-verified)'.

Johnson & Johnson alleged that the presentation of the pie charts invited a comparison between the various success rates across the three charts. It was an established principle under the Code that apparent differences in graphically presented data were assumed to be statistically significant unless stated otherwise. The presentation of the data in this case implied that Champix was significantly more effective than other treatments. Since no statistical analysis was presented on the pie charts, or within the original NHS data, the statistical significance was not proven. This fact was not clear. Johnson & Johnson alleged that the figure had not been presented in such a way as to give a clear, fair and balanced view of the matter with which it dealt.

It was generally accepted that data presented in promotional material was taken from prospective, randomised clinical trials unless otherwise stated. The NHS data was taken from a retrospective database audit and this had not been made sufficiently clear.

Johnson & Johnson alleged that the presentation of the pie charts was misleading and that insufficient information was provided for the reader to form their own opinion of the therapeutic value of the medicine.

The Panel noted that the data was referenced to statistics on NHS Stop Smoking Services: England, April 2007 – March 2008, a statistical bulletin published by the NHS Information Centre which featured data on people who had received support to quit smoking via a range of NHS Stop Smoking Services. The report stated that varenicline was the

most successful pharmacotherapy used to help people quit in 2007/08 with almost two-thirds of people using it successfully quitting. Of those who set a quit date and used Champix (n=97,259), 63% successfully quit compared with 53% on bupropion (n=22,234) and 49% who were on NRT (n=474,311). Of those who did not receive any type of pharmacotherapy, 55% successfully quit. Among the pharmacotherapies used 66% of people who set a quit date successfully quit using NRT only. The Panel noted the regional, gender and other differences highlighted in the report. The Panel noted, as submitted by Pfizer, that the report was not an interventional trial with statistical analysis but provided data to support clinical trial evidence and was of interest to health professionals. The Panel considered that readers had to be provided with sufficient information about the data such that they could assess the claims made.

The Panel considered that by placing the pie charts immediately adjacent to each other the material invited the reader to directly compare the quit rates and implied that there was an actual difference between the products. This had not been shown as there was no statistical analysis. The statistical analysis on the previous page had shown a difference between Champix and NiQuitin CQ Clear at 12 weeks but not at 1 year. The data related to those who set a quit date and self-reported as having quit at the 4 week follow up. Validation of the quit attempt by CO confirmation did not occur if the intervention was by telephone. Overall 31% of people who set a quit date successfully quit confirmed by CO validation. The information provided about the observational data was wholly inadequate. The footnote was insufficient in that regard. A reader might mistakenly assume that the data was derived from a published clinical study. The comparison was misleading as alleged. Breaches of the Code were ruled.

Johnson & Johnson noted that the presentation of the pie charts excluded the data relating to the percentage of successful quitters where no pharmacotherapy was provided. Had this data been presented, it would have been clear that the success rate for 'no pharmacological treatment' (55%) was seemingly as effective as both NRT and bupropion. This cast serious doubt over the validity of the results as NRT and bupropion were established efficacious treatments for nicotine dependence. This data was not provided and the omission was therefore misleading. Johnson & Johnson alleged that the information presented was incomplete and therefore the recipient would be unable to form their own opinion of the therapeutic value of the medicine.

The Panel noted its comments about the report and data above. The Panel noted Johnson & Johnson's submission that NRT and bupropion were established efficacious treatments for nicotine dependence. The Panel considered it would thus have been helpful to include data on those (55%) who successfully quit without pharmacotherapy. It was not clear whether people who did not receive pharmacotherapy would receive advice from the stop smoking service and whether it was this advice that had motivated smokers to quit. Given that the page was headed 'Champix and the NHS Stop Smoking Service' the Panel considered that the omission of the data was misleading as alleged such that the reader had insufficient information to assess the data presented; a breach of the Code was ruled.

Johnson & Johnson alleged that the headline above the pie charts, 'Champix and the NHS stop smoking service', strongly implied that the NHS endorsed the use of Champix over and above other smoking cessation therapies. This was compounded by the presentation of the data which displayed the pie chart relating to Champix first despite the fact that many more patients were treated with NRT. Johnson & Johnson also noted that underneath the pie charts, 'CHAMPIX' appeared in prominent blue capital letters whereas NRT and bupropion appeared less prominently in grey. Although the reader could be misled into believing that Champix was the NHS Stop Smoking Service medicine of choice, this was clearly not the case as only 14% of patients received it.

In summary, for the reasons outlined above, Johnson & Johnson alleged the page was misleading and implied that the NHS Stop Smoking Service endorsed Champix over and above other pharmacotherapies. This was unsupported by the data and was therefore misleading.

The Panel noted the page heading 'Champix and the NHS Stop Smoking Service'. The Panel further noted that the phrase 'NHS stop smoking service' appeared in a green font, the same shade as the Champix data in the pie chart beneath. However the Panel did not consider that the use of colour, the heading or the page overall directly or indirectly implied NHS endorsement of Champix as alleged. Rather the page purported to reflect the Champix data published in the report. The page was not misleading on this point as alleged. No breach of the Code was ruled.

The advertisement, headed 'New NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10', featured a bar chart which compared the relative impact of 3 stop smoking interventions (no support; individual behavioural support and group behavioural support) combined with no medication, NRT, bupropion or Champix on 4 week quit rates. The heading and bar chart were each asterisked to a footnote which cited the NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10. Adjacent to the bar chart were three bullet points: two highlighted Department of Health (DoH) guidance whilst the third read 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons between treatments across different settings. The 4 week quit rates have not been measured directly but

have been extrapolated from longer term quit rates'. The claim 'Champix – An evidenced-based choice in smoking cessation' ran below the text described above followed by the prescribing information. The product logo appeared in the bottom right hand corner.

Johnson & Johnson alleged that the heading, combined with the overall layout of the advertisement was extremely confusing and misleading. The overall impression was that the advertisement was guidance from the NHS Stop Smoking Service and that the service recommended use of Champix over and above other pharmacotherapies. The impression that the advertisement was NHS guidance was compounded by the statement (which appeared as the third of three bullet points beneath the heading) 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons …'. The word 'this' implied that the advertisement itself was the guidance.

Johnson & Johnson alleged that in addition, the only text-based reference to Champix 'An evidence-based choice in smoking cessation', in association with the heading, clearly implied that the NHS Stop Smoking Services recommended Champix over and above other treatments. This was not true. Indeed, the NHS Service and Monitoring Guidance 2009/10 stated that NRT, Champix and bupropion should all be made available first line.

Johnson & Johnson alleged that the overall impression of the advertisement was ambiguous and therefore misleading.

The Panel noted that the NHS Service and Monitoring Guidance stated that Champix had been proven to be a highly cost-effective treatment resulting in average success rates of 61% at 4 weeks in the first and second quarters of 2008/2009. All motivated quitters should be given the optimum chance of success in any quit attempt and NRT, Champix and bupropion should all be made available in combination with intensive behavioural support as first-line treatments (where clinically appropriate).

The Panel considered that although the heading 'NHS Stop Smoking Services:' appeared in a green font, the same shade as the Champix data in the bar chart, readers would not assume that the advertisement was the official NHS Guidance or that Champix was its medicine of choice as alleged. It was clearly an advertisement for Champix. It featured promotional claims and prescribing information. No breach of the Code was ruled.

Johnson & Johnson noted that the bar chart was referenced to the NHS Stop Smoking Services: Services and monitoring Guidance 2009/10 and was titled 'The relative impact of a variety of evidence-based stop smoking interventions and pharmacotherapies upon 4 week quit rates'. The heading of the bar chart clearly indicated that the data portrayed the 'relative impact' of stop smoking interventions. 'Relative' emphasised the intention to draw a direct comparison between the treatments presented. However, any such comparison would be meaningless as there was no indication as to whether the differences were statistically significant. In addition, there were no patient numbers presented in the bar chart. This meant that the reader could not judge the context of the data. Johnson & Johnson alleged that the bar chart was misleading.

The Panel noted, as stated in a very small footnote beneath the bar chart, that it was adapted from the Cochrane database of systematic reviews. It had been reproduced from the NHS stop smoking services: Services and Monitoring Guidance 2009/10. The bar chart invited the reader to directly compare the 4 week quit rates of each medicine and no medication when used in combination with 3 different evidenced based interventions. Champix had the most favourable outcome with each intervention. Further details about the Cochrane analysis were given in the third bullet point.

The Panel considered that the bar chart implied that in relation to each intervention statistically significantly more smokers quit with Champix than with any other treatment regimen. That was not necessarily so. The statistical significance of the data was unknown. The bar chart was misleading in this regard. Breaches of the Code were ruled.

Johnson & Johnson noted that the third bullet point read 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons between treatments across different settings. The 4 week quit rates have not been measured directly but have been extrapolated from longer term quit rates.' The Cochrane Reviews upon which these data were based appraised studies with a 6 month data point. It was therefore unclear either from the material or the source reference, how the 4 week data were calculated and whether the method used had suitable scientific validity for inclusion within promotional material. Pfizer had failed to explain the basis of this extrapolated data, other than to state that the authors were reputable and credible and hence it believed the data to be valid. Johnson & Johnson alleged that this was insufficient as Pfizer was unable to substantiate the exact methods used to extrapolate the four week data.

Johnson & Johnson alleged that the extrapolation of data to a 4 week comparison without clear explanation or substantiation was misleading. The basis for the 4 week data had not been made sufficiently clear. The advertisement was thus misleading. Additionally the 4 week data was not available and therefore could not be substantiated.

The Panel noted its rulings and comments above. The Panel had concerns about the data. The Panel considered that the third bullet point made it clear

that the 4 week quit rates had been extrapolated from longer term quit rates based on indirect comparisons between treatments across different settings. The Panel did not have a copy of the Cochrane reviews. On the evidence before it the Panel did not consider that it was necessary to provide further information about the calculation of the 4 week quit rates in the advertisement as alleged. The basis of the data was clear. No breach of the Code was ruled on this very narrow point.

The Panel agreed with Pfizer that it was not for the authors of the NHS guidance to substantiate their data. The Code required that companies must be able to substantiate information, claim or comparisons and such data be provided on request from a health professional. The data presented in Pfizer's advertisement had to be capable of substantiation. The authors of the NHS guidance had extrapolated long term data published in the Cochrane reviews to a 4 week time point. No details about the calculation and any assumptions made were published in the NHS guidance document.

The Panel considered the allegation that Pfizer was unable to substantiate the four week data. The Panel noted the supplementary information to the Code listed 'statistical information' as an area where particular care should be taken. This stated, *inter alia*, 'Care must be taken to ensure that there is a sound statistical basis for all information, claims and comparisons in promotional material.' It continued 'Instances have occurred where claims have been based on published papers in which the arithmetic and/or statistical methodology was incorrect. Accordingly, before statistical information is included in promotional material it must have been subjected to statistical appraisal'. The Panel considered that Pfizer's position, that it did not believe it would be expected to ask the authors of the NHS guidance, all of whom were recognised experts in the field of smoking cessation, to substantiate their data was unacceptable. It was Pfizer's responsibility to ensure that it could substantiate all claims and data in its promotional material irrespective of the source of such data. Thus, in the Panel's view, Pfizer should have satisfied itself that the extrapolation of the 4 week quit rates from longer term quit data was capable of substantiation before using such data in promotional material. Pfizer had not provided any data or detail about this calculation and thus the Panel considered that Pfizer had not substantiated the calculation of the 4 week quit rates. A breach of the Code was ruled.

Johnson & Johnson Limited complained about the promotion of Champix (varenicline) by Pfizer Limited. The items at issue were a leavepiece (ref CHA693) available from a stand at a Nursing in Practice event held in April 2009 and an advertisement (ref CHA752a) published in GP, 12 June 2009.

Champix was indicated for smoking cessation.

As the complaint involved an alleged breach of undertaking that element was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

A Champix leavepiece (ref CHA693)

The leavepiece was entitled 'How you and 12 weeks of Champix can aid smoking cessation with your patients'.

1 Alleged breach of undertaking

COMPLAINT

Johnson & Johnson noted that in Case AUTH/2203/1/09 the Panel upheld a complaint regarding the claim 'Champix at 12 weeks provides significantly greater quit success vs. NRT [nicotine replacement therapy] (NiQuitin CQ Clear)' and the use of Aubin *et al* (2008) to support it.

In Case AUTH/2203/1/09 the Panel had stated that: '… whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data. The Panel noted the study authors' conclusions that "motivational influences are likely to exist in a real-world setting and the outcomes of this study show that varenicline is more effective than transdermal nicotine in enhancing quit rates in an open-label setting". The Panel did not consider that the claim at issue was a fair reflection of the study findings in this regard. The main body of the advertisement gave no relevant details about the study design and so the reader would be unaware of the basis of the data'.

Johnson & Johnson stated that the Panel ruled that, when Aubin *et al* was cited in promotional material, it should be accompanied by sufficient information in order that readers could assess the data. The Panel made particular reference to the authors' conclusions that motivational factors were affected by the open-label setting and commented that the main body of the advertisement contained no relevant details regarding the study design. This meant that readers would be unaware of the basis for the data.

Johnson & Johnson noted that in the leavepiece now at issue, a full page was dedicated to a comparison between Champix and NRT. The page was headed 'Prescribe 12 weeks of Champix for your motivated quitters' and included a bar chart seemingly comparing Champix and NRT at 12 weeks. Below the bar chart were a number of claims relating to the comparison. Johnson & Johnson was concerned about the presentation of the Aubin *et al* data.

Johnson & Johnson alleged that although the footnote provided further details about the study, including study design, patient numbers, study

duration and primary and secondary endpoints, this did not go far enough. It was clear from the Panel's ruling in Case AUTH/2203/1/09 that any necessary additional information about the study should be included in the body of the advertisement. Providing further information about the study only by way of a footnote was not consistent with the previous Panel ruling.

Johnson & Johnson also alleged that a major issue with Aubin *et al* was that previous treatment might have influenced patient motivation – it was well known that motivation played a role in the success of quit attempts. The importance of previous treatment would be particularly relevant in the context of an open-label study where the subjects would have known which treatment they were receiving. It was highly likely that any such bias would have favoured the new treatment (Champix) as it would have been viewed by subjects, and perhaps investigators, as 'novel' and, possibly, an 'advance' in smoking cessation. That Champix was a prescription only medicine and NRT had been available over the counter for many years might also have been significant. An exclusion for patients who had used NRT within the previous 6 months was not rigorous enough to ensure that previous NRT treatment did not bias the result in favour of Champix.

Johnson & Johnson alleged that this potential difference in motivation between the groups was demonstrated by the fact that 9 (2%) subjects dropped out of the study when randomised to NRT compared with 2 (0.5%) randomised to Champix. This was acknowledged by the authors who stated 'A limitation of this study was the open-label design. The differential dropout rate after medication assignment and before the first dose of treatment suggests that some motivational bias may have influenced the results'.

In inter-company dialogue Pfizer stated that due to randomisation, it was likely that there were similar numbers of patients who had previously used NRT in both treatment groups. Johnson & Johnson disagreed as only the NRT treatment arm would be negatively biased as a result of previous treatment, and subsequent failure, with NRT.

Despite the Panel's ruling that sufficient information relating to the nature of the Aubin data should be included in promotional material, Johnson & Johnson noted that there was no reference to the fact that almost 50% of all study participants had already received NRT and the potential impact of this upon the results. Therefore, not all relevant information had been presented.

Moreover, the footnote on the summary page headed '12 weeks of Champix with quit support helps smokers break their addiction' contained even less information about the study. In particular, there was no mention of its open-label nature.

In summary, Johnson & Johnson alleged that Pfizer's use of a footnote to provide further information about Aubin *et al* was inconsistent with the Panel's ruling which suggested that it should be included as part of the main body of the advertisement. In addition, inadequate information had been provided to explain the failings of the study in particular around issues of previous treatment and ultimately motivation. Finally, Johnson & Johnson was concerned that the leavepiece summary page provided only very limited information about the study and did not clarify that it was open-label in design.

Johnson & Johnson thus alleged that Pfizer had not complied with the undertaking given in Case AUTH/2203/1/09 in breach of Clause 25 of the Code. In addition, the material was misleading and did not enable the recipient to form their own opinion of the therapeutic value of the medicine in breach of Clause 7.2.

In addition to those clauses cited by Johnson & Johnson the Authority asked Pfizer to respond in relation to the requirements of Clauses 2 and 9.1.

RESPONSE

Pfizer noted that Case AUTH/2203/1/09 concerned the claim 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' in an advertisement. The Panel had stated that: '… whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data'.

In light of this case and its undertaking, Pfizer reviewed all promotional material containing data from Aubin *et al* and immediately withdrew any that was non compliant. During this review Pfizer wanted to ensure that the design of Aubin *et al* was clearly described with sufficient information about the study to enable readers to assess the data. In the leavepiece at issue, the study was described as: 'Aubin H-J *et al*. An open label, randomised, multicentre clinical trial of 746 smokers directly compared the recommended treatment courses of Champix for 12 weeks with the NRT patch (NiQuitin CQ Clear) for 10 weeks. The primary endpoint was the continuous abstinence rate (CO [carbon-monoxide]-confirmed) at weeks 9-12 for Champix and at weeks 8-11 for NRT. A secondary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-52 for Champix and at weeks 8-52 for NRT'.

Pfizer submitted that the description made clear that this was an open-label study; the recommended treatment courses for each product – 12 weeks for Champix and 10 for the NRT patch, as per the respective summaries of product characteristics (SPCs); the primary endpoint was assessed at the end of the last 4 weeks of treatment for both products, ie weeks 9-12 for Champix and 8-11 for the NRT patch and the NRT patch used was NiQuitin CQ Clear.

Pfizer submitted that it was standard and acceptable practice to describe the study designs in this format on a page such as this in a leavepiece. Footnotes were not prohibited by the Code and could be used to provide additional information, but only if this information did not alter the interpretation. A misleading headline could not be corrected by a footnote.

Pfizer submitted that the presentation of the study design in this leavepiece was appropriate, not misleading and was not in breach of its undertaking. In this regard it submitted that there had been no breach of Clauses 7.2 or 25. High standards had been maintained (Clause 9.1) and the leavepiece had not brought the industry into disrepute (Clause 2).

With regard to the comments about the fact that almost half of the subjects had previously tried to quit and failed using a transdermal nicotine patch and that this might have favoured Champix, Pfizer submitted that patients were excluded if they had used NRT within the previous 6 months. In addition, treatment by baseline covariate analysis demonstrated that there was no interaction (p>0.10) with prior quit attempt using NRT or transdermal patch, suggesting that this did not influence the efficacy results. In other words, if there was significant motivational bias in this study then those patients who had previously tried NRT should have demonstrated a greater benefit from Champix vs NRT than those patients who had never tried NRT. This was not shown; the benefit of Champix vs NRT was the same regardless of prior NRT use. Pfizer agreed that if there had been a significant interaction with prior NRT use then this should have been presented in the material but as there was no significant interaction this data was not presented.

Pfizer submitted that the leavepiece summary page was a summary of material from the leavepiece itself, it was not necessary to repeat everything again on the summary page, it was made clear in the footnote that the primary endpoint for Champix was at weeks 9-12 and for NRT at weeks 8-11. Pfizer had also reminded the reader that the NRT patch used was NiQuitin CQ Clear. Aubin *et al* was cited at the bottom of the summary page and was described as: 'Aubin H-J *et al*. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial. Thorax 2008; 63:717-724'.

PANEL RULING

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

The Panel noted that the first page at issue in the leavepiece (the inside central page) was headed 'Prescribe 12 weeks of Champix for your motivated quitters 5*' beneath which was a bar chart which compared the continuous abstinence rate in the last 4 weeks of treatment of Champix (55.9%) with that of an NRT patch (43.2%) at 12 weeks. The bar chart was headed 'Champix vs. NRT patch at 12 weeks (NiQuitin CQ Clear) (N=746) 5*'. Three bullet points followed beneath the bar chart including: 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' and 'At 1 year, the quit rate was 26.1% for Champix vs. 20.3% for NRT patch (p=0.056, not significant)'. All the data was referenced to Aubin *et al* (reference 5). The asterisk by the two claims took readers to a footnote at the bottom of the page, 'Aubin H-J *et al*. An open label, randomised, multi-centre clinical trial of 746 smokers directly compared the recommended treatment courses of Champix for 12 weeks with the NRT patch (NiQuitin CQ Clear) for 10 weeks. The primary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-12 for Champix and at weeks 8-11 for NRT. A secondary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-52 for Champix and at weeks 8-52 for NRT'.

Less information about Aubin *et al* appeared on the summary page which was headed '12 weeks of Champix with quit support helps smokers break their addiction' and featured 3 bullet points including the claim 'Significantly higher quit rate at 12 weeks versus NRT patch* (NiQuitin CQ Clear), bupropion and placebo4, 5**'. The comparison with NRT patch was referenced to Aubin *et al* and that with bupropion and placebo was referenced to Nides *et al* (2008). Two footnotes gave limited details about each study; that for Aubin *et al* described its primary and one secondary endpoint, continuous abstinence rate.

The Panel noted that the previous case, Case AUTH/2203/1/09, concerned a journal advertisement wherein the claim 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' was ruled in breach of Clause 7.2. The substantiating data was Aubin *et al*, limited details of which appeared as a footnote to a separate claim. The footnote explained that the recommended treatment course for Champix was 12 weeks and for NRT patch (NiQuitin CQ Clear) was 10 weeks. Continuous abstinence rate was CO-confirmed at weeks 9-12 for Champix and at weeks 8-11 for NRT. No further details about Aubin *et al* appeared in the advertisement. The relevant part of the Panel ruling in Case AUTH/2203/1/09 is reproduced below.

> 'The Panel noted that Aubin *et al* was an open-label, randomised trial to compare a 12 week standard regimen of Champix with a 10 week standard regimen of NRT for smoking cessation. All patients were motivated to quit and had not used any form of NRT in the previous 6 months. The study authors referred to the intent to treat analysis as a gold standard and explained that they reported the primary analysis population (those who were randomised and took at least one dose of medicine) in the efficacy results as

this was the study's prespecified primary analysis population. The authors noted that this might underestimate the efficacy of Champix relative to NRT because of differential drop out after medication assignment.

The Panel noted each party's submission about the study methodology and limitations. The study authors noted that a limitation of the study was its open-label design and a detailed discussion of the study's limitations appeared in the published paper. The Panel noted the study authors' comment that technical problems made it difficult to create NRT and placebo patches that were indistinguishable in appearance and odour.

The Panel noted that whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data. The Panel noted the study authors' conclusions that 'motivational influences are likely to exist in a real-world setting and the outcomes of this study show that varenicline is more effective than transdermal nicotine in enhancing quit rates **in an open-label setting**' (emphasis added). The Panel did not consider that the claim at issue was a fair reflection of the study findings in this regard. The main body of the advertisement gave no relevant details about the study design and so the reader would be unaware of the basis of the data. The Panel considered the claim 'Champix at 12 weeks provides significant greater quit success vs NRT (NiQuitin CQ Clear)' was misleading in this regard and a breach of Clause 7.2 was ruled.'

Turning to the present case, Case AUTH/2259/8/09, the Panel noted that there were differences between the claim at issue previously 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' and the two pages in the leavepiece now at issue. The claim at issue previously was not reproduced in the leavepiece although, in the Panel's view the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch ($p<0.001$)' was closely similar. The issue was whether sufficient details about Aubin *et al* had been given such that the leavepiece was not caught by the undertaking previously given. The Panel noted that the only details about the study design for Aubin *et al* appeared in footnotes. The footnote on the inside central page mentioned the open-label design, that on the summary page did not. The Panel noted that claims in promotional material should be capable of standing alone as regards the requirements of the Code. Information integral to a reader's understanding of a claim should not be relegated to a footnote, it should appear in the immediate visual field of the claim itself. The open-label nature of the study was a very relevant factor for readers in assessing the claims at issue in both cases. The Panel noted that whilst changes had been made to the material these were insufficient to address the concerns raised by the Panel previously. Whilst it was of course not necessary to detail every aspect of the study, sufficient information should be given such that the reader was aware of the basis of the data. Pertinent information about Aubin *et al* was not an integral part of the main body of the pages at issue in the leavepiece. The footnotes were insufficient in this regard. The leavepiece was thus caught by the undertaking previously given. A breach of Clause 25 was ruled. High standards had not been maintained and the material brought discredit upon and reduced confidence in the pharmaceutical industry; breaches of Clauses 9.1 and 2 were ruled.

The Panel noted its comment above about the use of footnotes. Overall, the Panel considered that insufficient information had been provided to enable a reader to form their own opinion of the therapeutic value of the medicine as alleged. A breach of Clause 7.2 was ruled.

2 Generalisation of data for NiQuitin CQ to all NRT patches

COMPLAINT

Johnson & Johnson alleged that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch ($p<0.001$)' was misleading and all-encompassing. The claim was referenced to Aubin *et al* wherein Champix was compared to the NiQuitin CQ Clear patch (manufactured by GlaxoSmithKline). The NiQuitin CQ Clear patch was a specific formulation which differed from other patches in terms of its release characteristics and pharmacokinetic profile. Johnson & Johnson alleged that the claim implied that all NRT patches were the same and that Champix had proven superiority over all patches. This had not been proven. On the contrary, there was no clinical efficacy data directly comparing Nicorette patch with any other NRT patch. In addition, Johnson & Johnson was unaware of any direct comparisons between Champix and any nicotine patch other than NiQuitin CQ Clear. Therefore, to imply that Champix was more effective than all NRT patches was misleading and disparaged other NRT patches including Nicorette.

Johnson & Johnson stated that it would be unacceptable to make broad generalisations relating to the efficacy of other classes of treatments. For instance, if a study suggested that a novel therapy was more effective than simvastatin in the treatment of hypercholesteraemia, it would not be acceptable to generalise that it was more effective than all other statins. Likewise, such generalisations were not acceptable for NRT where products were available at a variety of strengths, with different dosing periods, release mechanisms, pharmacokinetics profiles and hence potentially efficacy rates. The generalisation of data for

NiQuitin CQ Clear to all NRT patches was repeated throughout the central page including the footnote.

In inter-company dialogue Pfizer had argued that as the title of the bar chart, which was the first substantive mention of the comparator, stated that this treatment was NiQuitin CQ Clear, it was not necessary to refer to it again. Johnson & Johnson alleged that the clarifying statement was not prominent enough to ensure that all readers would, at a glance, know that the patch used was NiQuitin CQ Clear. Indeed, if Pfizer had wanted readers to be in no doubt as to the nature of the patch, then it could have referred to the product by name throughout the leavepiece. Although Pfizer had not explicitly categorised NRT patches as the same, there was a clear implication that the results presented related to all NRT patches.

Johnson & Johnson therefore alleged that Pfizer had failed to take into account differences between NRT patches and the leavepiece was therefore misleading and the information presented was not accurate, balanced, fair and unambiguous. A breach of Clause 7.2 was alleged.

RESPONSE

Pfizer noted that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was the first bullet point beneath the bar chart. The title of the bar chart clearly stated that the NRT patch used was NiQuitin CQ Clear. This was the first substantive mention of the comparator so it therefore followed that all future references on the same page summarising the same study and the same data referred to the NiQuitin CQ Clear patch. Precisely because Pfizer did not want to mislead the reader into thinking this data applied necessarily to all NRT patches it had been careful to highlight NiQuitin CQ Clear patch at the first substantive mention in the bar chart's title. Pfizer had also stated NiQuitin CQ Clear in the description of the study design. Pfizer had not referred to, or categorised NRT patches to be the same.

As the type of patch was clearly and accurately specified in the title of the bar chart and in the description of the study, Pfizer submitted that the claim was not all-encompassing, misleading, or disparaging or that there had been a breach of Clause 7.2.

PANEL RULING

The Panel noted that the only references to NiQuitin CQ Clear were in the heading to the bar chart and once in the footnote at the bottom of the page. All other references on the page, including other labelling on the bar chart, were to 'NRT patch'. The Panel did not accept Pfizer's submission that it followed that after the first substantive mention of the comparator treatment all future references to 'NRT patch' would, in effect, mean NiQuitin CQ Clear. That was not necessarily so. The relevant bar of the bar chart was labelled 'NRT patch'. Further, given that no information about the study design appeared in the body of the page, a reader might assume there was more than one arm of the study and thus more than one NRT comparator. The position was not clear.

The Panel noted Johnson & Johnson's submission that there was no direct comparative efficacy data between Nicorette and any other NRT patch and that the NiQuitin CQ Clear patch differed from other patches in terms of its release characteristics and pharmacokinetic profile. Overall, the Panel considered that in the context in which it appeared the claim at issue could not take the benefit of the reference to NiQuitin CQ Clear in the title of the bar chart as submitted by Pfizer. Claims had to be able to stand alone under the Code. The Panel considered that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' was misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel noted that in addition Johnson & Johnson had alleged that the claim disparaged other NRT patches including Nicorette but had omitted to cite a clause number, in this instance Clause 8.1, as required under Paragraph 5.2 of the Constitution and Procedure. No ruling was thus made on this point.

3 Difference in treatment times for NiQuitin CQ Clear and Champix

COMPLAINT

Johnson & Johnson noted that the claim 'Champix at 12 weeks enabled significantly more smokers to quit than those who used NRT patch (p<0.001)' related to differences in treatment timing between NiQuitin CQ Clear and Champix. Johnson & Johnson alleged that readers should have been made aware of this. In Aubin *et al*, the primary endpoint was continuous abstinence rates for Champix at weeks 9-12 and for NiQuitin CQ at weeks 8-11. Treatment duration in the Champix group was 12 weeks, compared with 10 weeks for the NRT group. These differences in treatment duration and measurement of the primary endpoint introduced a potential source of bias.

Pfizer had clarified that a footnote explained both the duration of treatment and the differences in the measurement of the primary endpoint (continuous abstinence in the last 4 weeks of treatment for both treatment arms – weeks 9-12 for Champix and weeks 8-11 for NRT). However, Johnson & Johnson alleged that the claim clearly stated 'Champix vs NRT patch at 12 weeks …' which was therefore incorrect. The heading of the graph immediately above the claim also inaccurately stated '12 weeks'.

Given this, both the claim and the title of the bar chart were inaccurate and inconsistent with Aubin

et al and the footnote in breach of Clause 7.2.

RESPONSE

Pfizer submitted that Aubin *et al* directly compared the recommended treatment courses for both treatments (as per their SPCs), which were 10 weeks of treatment for NiQuitin CQ Clear and 12 for Champix. This was stated clearly on the page '… recommended treatment courses of Champix for 12 weeks with the NRT patch (NiQuitin CQ Clear) for 10 weeks. The primary endpoint was the continuous abstinence rate (CO-confirmed) at weeks 9-12 for Champix and at weeks 8-11 for NRT'. In addition, the differences when measuring the secondary endpoint, ie 9-52 weeks for Champix vs 8-52 weeks for NRT were also explained.

Pfizer submitted that in addition, a pre-specified sensitivity analysis compared, like for like, 4 week continuous abstinence rates for weeks 9–12 in both treatment groups and weeks 8–11 in both treatment groups. The results showed that the conclusions of the study remained unchanged. In other words there was no evidence that comparing the recommended treatment regimens as per the SPC for each product had introduced bias, whether compared at the end of treatment for each regimen or at the same time point for each regimen.

Pfizer submitted that referring to 'Champix at 12 weeks' was appropriate as this was the recommended treatment regimen in the SPC and the duration of Champix treatment in Aubin *et al*. As the study treatment duration and continuous abstinence rates for both primary and secondary endpoints were clearly stated on the page and clearly referenced to Aubin *et al*, Pfizer submitted that it had given accurate, balanced, fair and objective results which were unambiguous and not misleading. Therefore, Pfizer denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the treatment periods of both NiQuitin CQ Clear and Champix in Aubin *et al* reflected that recommended in their SPCs. The Panel noted that the 12 week treatment period for Champix was referred to in the prominent page heading 'Prescribe 12 weeks of Champix for your motivated quitters', again in the title of the bar chart and in the first bullet point. A reference also appeared in the footnote. Comparable information for NiQuitin CQ Clear was not given in the main body of the page. The Panel noted its comments about footnotes above. Whilst the footnote made it clear, *inter alia*, that Aubin *et al* examined NiQuitin CQ Clear for its recommended treatment period of 10 weeks and made clear the differences in the measurement of the primary endpoint the Panel considered that the relegation of this information to a footnote meant that overall the page gave a misleading impression of the treatment duration and measurement of the primary endpoint for NiQuitin CQ. A breach of Clause 7.2 was ruled.

4 Presentation of the pie charts showing 4 week quit rates and use of audit data

Beneath the heading 'Champix and the NHS stop smoking service' appeared a highlighted box featuring 3 pie charts headed 'Successful quitters at week 4 follow-up by treatment used (April 2007 – March 2008)'. The pie charts depicted separately the percentage of successful quitters for Champix (63%, n=97,259); NRT (49%, n=474,311) and bupropion (53%, n=22,348). The heading was asterisked to a footnote at the bottom of the page which read 'Based on a statistical report presenting final results from the monitoring of the NHS Stop Smoking Service from the period April 2007 – March 2008. Successfully quit = not smoking at the 4 week follow up (self-reported, not necessarily CO-verified)'.

COMPLAINT

Johnson & Johnson alleged that the presentation of the pie charts within a single frame invited a comparison between the various success rates across the three charts.

Johnson & Johnson stated that it was an established principle under the Code that apparent differences in graphically presented data were assumed to be statistically significant unless stated otherwise. The presentation of the data in this case implied that Champix was significantly more effective than other treatments. Since no statistical analysis was presented on the pie charts, or within the original NHS data, the statistical significance was not proven. This fact was not made clear to the reader.

In inter-company dialogue Pfizer had argued that it had simply represented the data from the NHS Stop Smoking Service report in an accurate, balanced, fair and objective manner. Johnson & Johnson disagreed. The fact that no statistics were available in the NHS reference did not make it acceptable to present data implying proven superiority of one treatment over another.

Johnson & Johnson alleged that the figure had not been presented in such a way as to give a clear, fair and balanced view of the matter with which it dealt and alleged a breach of Clauses 7.2 and 7.8.

It was generally accepted that data presented in promotional material was taken from prospective, randomised clinical trials unless otherwise stated. The NHS data was taken from a retrospective database audit and this had not been made sufficiently clear.

Pfizer had argued that the heading of the page, the title of the pie chart and the further information on the page made it very clear as to where the data was from. Johnson & Johnson disagreed. Neither the page heading nor the pie chart title referred to the nature of the data cited. The footnote stated that the charts were 'Based on a statistical report presenting final results from the monitoring of the

NHS Stop Smoking Service from the period April 2007 – March 2008'. However, Johnson & Johnson alleged that this statement was not prominent enough to make this clear to the reader, as the footnote was in a small, pale grey font. The overall impression of the page was such that the reader could easily assume that the data presented was derived from a clinical trial.

Johnson & Johnson alleged that the presentation of the pie charts was misleading and that insufficient information was provided for the reader to form their own opinion of the therapeutic value of the medicine in breach of Clause 7.2.

RESPONSE

Pfizer submitted that these data had been taken from a report from the monitoring of the NHS Stop Smoking Service for the period April 2007 to March 2008. Successful quitters were defined in the report as not smoking at the 4 week follow up based on self reporting and not necessarily CO verified. It was clear that this was not an interventional clinical trial, but an NHS report of real world results over a 12 month period for the 3 smoking cessation treatments. As this was not a clinical trial with an a *priori* hypothesis being tested there was no statistical analysis. Pfizer had presented the data reported by the NHS which was in the public domain, and which was updated on an ongoing basis. Reporting real world data on medicines as they were used in practice was an important addition to reporting efficacy results as found in clinical trials. Pfizer had described the results of Aubin *et al* on the previous page and had referenced the body of clinical trial evidence (Aubin *et al*, Gonzalez *et al* 2006, Nides *et al*, Jorenby *et al* 2008) for Champix. The NHS report provided further supporting data to the clinical trial evidence and was a document that was from a reputable source and was of interest to health professionals who worked in the field of smoking cessation. Pfizer submitted that it had represented the data in an accurate, balanced, fair and objective manner, and therefore denied breaches of Clauses 7.2 and 7.8.

PANEL RULING

The Panel noted that the data was referenced to statistics on NHS Stop Smoking Services: England, April 2007 – March 2008, a statistical bulletin published by the NHS Information Centre which featured data collected on people who had received support to quit smoking via a range of NHS Stop Smoking Services. The report stated that varenicline was the most successful pharmacotherapy used to help people quit in 2007/08 with almost two-thirds of people using it successfully quitting. Of those who set a quit date and used Champix (n=97,259), 63% successfully quit compared with 53% on bupropion (n=22,234) and 49% who were on NRT (n=474,311). Of those who did not receive any type of pharmacotherapy, 55% successfully quit. Among the pharmacotherapies used 66% of people who set a quit date successfully quit using NRT only. The Panel noted the regional, gender and other differences highlighted in the report. The Panel noted, as submitted by Pfizer, that the report was not an interventional trial with statistical analysis but provided data to support clinical trial evidence and was of interest to health professionals. The Panel considered that readers had to be provided with sufficient information about the data such that they could assess the claims made.

The Panel considered that by placing the pie charts immediately adjacent to each other the material invited the reader to directly compare the quit rates and implied that there was an actual difference between the products. This had not been shown as there was no statistical analysis. The statistical analysis on the previous page had shown a difference between Champix and NiQuitin CQ Clear at 12 weeks but not at 1 year. The data related to those who set a quit date and self-reported as having quit at the 4 week follow up. Validation of the quit attempt by CO confirmation did not occur if the intervention was by telephone. Overall 31% of people who set a quit date successfully quit confirmed by CO validation. The information provided about the observational data was wholly inadequate. The footnote was insufficient in that regard. A reader might mistakenly assume that the data was derived from a published clinical study. The comparison was misleading as alleged. Breaches of Clauses 7.2 and 7.8 were ruled.

During its consideration of this point the Panel was extremely concerned about the presentation of data from the bulletin: statistics on NHS stop smoking services April 2007 to March 2008. The data was self reported and not necessarily CO verified. The group sizes differed markedly. That 55% who received no medication successfully quit meant that overall the audit data should be viewed with a degree of circumspection. Companies should be extremely cautious when using such data. In the Panel's view it should not be used directly or indirectly to compare the clinical effectiveness of products or otherwise support clinical claims. There was no allegation on these points before the Panel. The Panel requested that both parties be advised of its views on this point which were also relevant to point 5 below.

5 Absence of relevant data

COMPLAINT

Johnson & Johnson noted that the presentation of the pie charts excluded the data relating to the percentage of successful quitters where no pharmacotherapy was provided. Had this data been presented, it would have been clear that the success rate for 'no pharmacological treatment' (55%) was seemingly as effective as both NRT and bupropion. This cast serious doubt over the validity of the results as it was well established that NRT and bupropion were efficacious treatments for nicotine dependence. This data was not provided and the

omission was therefore misleading.

Pfizer had argued that the data presented represented 'treatment used' and that the data were collected via standard methodology by the NHS Stop Smoking Services as recommended by the DoH. Nevertheless, Johnson & Johnson alleged that the absence of data for 'no pharmacological treatment' (which showed significant cessation rates) meant that the reader did not have sufficient information to draw their own conclusion about the validity of the data.

Johnson & Johnson alleged that the information presented was incomplete and therefore the recipient would be unable to form their own opinion of the therapeutic value of the medicine. Therefore, Johnson & Johnson alleged this was a breach of Clause 7.2.

RESPONSE

Pfizer pointed out that the pie charts were entitled 'Successful quitters at 4 week follow-up **by treatment** used (April 2007 - March 2008)' (emphasis added) thus the data presented was for quitters that took pharmacotherapy. The artwork presented on this page was a faithful representation of treatment used as presented by the NHS Stop Smoking Service report and gave an accurate, balanced, fair and objective view of the data. Pfizer did not agree that Clause 7.2 had been breached.

PANEL RULING

The Panel noted its comments about the report and data in point 4 above. The Panel noted Johnson & Johnson's submission that NRT and bupropion were established efficacious treatments for nicotine dependence. The Panel considered it would thus have been helpful to include data on those (55%) who successfully quit without pharmacotherapy. It was not clear whether people who did not receive pharmacotherapy would receive advice from the stop smoking service and whether it was this advice that had motivated smokers to quit. Given that the page was headed 'Champix and the NHS Stop Smoking Service' the Panel considered that the omission of the data was misleading as alleged such that the reader had insufficient information to assess the data presented; a breach of Clause 7.2 was ruled.

The Panel's views about use of the data in point 4 above also applied here.

6 Implied NHS endorsement

COMPLAINT

Johnson & Johnson alleged that the headline above the pie charts, 'Champix and the NHS stop smoking service', strongly implied that the NHS endorsed the use of Champix over and above other smoking cessation therapies. This was compounded by the presentation of the data which displayed the pie chart relating to Champix first despite the fact that many more patients were treated with NRT. Johnson & Johnson also noted that underneath the pie charts, 'CHAMPIX' appeared in capital letters and in a prominent blue font, whereas NRT and bupropion appeared less prominently in grey. Although the reader could be misled into believing that Champix was the NHS Stop Smoking Service medicine of choice, this was clearly not the case as only 14% of patients received it.

In summary, for the reasons outlined above, Johnson & Johnson alleged the page was misleading and implied that the NHS Stop Smoking Service endorsed Champix over and above other pharmacotherapies. This was unsupported by the data and was therefore misleading in breach of Clause 7.2.

RESPONSE

Pfizer did not agree that the headline implied that Champix was the medicine of choice of the NHS Stop Smoking Services. The headline pointed to the information below, which was the 4 week quit rates for all treatments, as reported by the NHS Stop Smoking Services. As the information detailed for all treatments was of equal size and proportion, Pfizer did not agree that this implied Champix was the medicine of choice. The charts presented not only the 4 week quit rates but also the number of smokers taking each smoking cessation treatment, clearly showing that the largest number (474,311 smokers) used NRT. Pfizer did not agree that a breach of Clause 7.2 had occurred.

PANEL RULING

The Panel noted the page heading 'Champix and the NHS Stop Smoking Service'. The Panel further noted that the phrase 'NHS stop smoking service' appeared in a green font, the same shade as the Champix data in the pie chart beneath. However the Panel did not consider that the use of colour, the heading or the page overall directly or indirectly implied NHS endorsement of Champix as alleged. Rather the page purported to reflect the Champix data published in the report. The page was not misleading on this point as alleged. No breach of Clause 7.2 was ruled.

B Champix journal advertisement (ref CHA752a)

1 Overall impression

COMPLAINT

The advertisement was entitled 'New NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10' referenced to the Department of Health (DoH) website. The text was broken over three lines with the largest font, highlighted in green, reserved for 'NHS Stop Smoking Services.'

Johnson & Johnson alleged that the heading, combined with the overall layout of the advertisement was extremely confusing and misleading. The overall impression was that the advertisement was guidance from the NHS Stop Smoking Service and that the service recommended use of Champix over and above other pharmacotherapies.

Johnson & Johnson alleged that the impression that the advertisement was NHS guidance was compounded by the statement (which appeared as the third of three bullet points beneath the heading) 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons …'. The word 'this' implied that the advertisement itself was the guidance.

Johnson & Johnson alleged that in addition, the only text-based reference to Champix 'An evidence-based choice in smoking cessation', in association with the heading, clearly implied that the NHS Stop Smoking Services recommended Champix over and above other treatments. This was not true. Indeed, the NHS Service and Monitoring Guidance 2009/10 stated that NRT, Champix and bupropion should all be made available first line.

Pfizer had submitted in the inter-company dialogue that the fact that the advertisement had both prescribing information and a Champix logo ensured that it simply served to create awareness of the NHS guidance. Johnson & Johnson disagreed. It was highly likely that many health professionals would be unaware that the inclusion of prescribing information and a product logo indicated that the item was an advertisement. Moreover, the inclusion of the Champix logo could serve to further the overall impression that Champix was the treatment of choice according to the NHS Stop Smoking Services guidance Johnson & Johnson alleged that the overall impression of the advertisement was ambiguous and therefore misleading in breach of Clause 7.2.

RESPONSE

Pfizer submitted that the advertisement was clearly for the new NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10 and was not the guidance itself. Half of the page consisted of prescribing information for Champix, the adverse event reporting box, references, a Champix logo, a Pfizer logo, a date of preparation and a Champix code. This did not look like an NHS document, nor did it have an official NHS logo.

Pfizer refuted that the advertisement misled the reader by suggesting that the service recommended use of Champix over and above other pharmacotherapies. The first bullet point of the advertisement stated 'To optimise success all recommended treatments will need to be offered as a first line intervention.'

Additionally, the claim 'Champix- An evidence-based choice in smoking cessation' was clearly referenced to the clinical trial evidence that supported it and it was an evidence based choice, not the evidence-based choice.

Pfizer did not agree that this was misleading and therefore denied a breach of Clause 7.2.

PANEL RULING

The advertisement headed 'New NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10' featured a bar chart which compared the relative impact of 3 stop smoking interventions (no support; individual behavioural support and group behavioural support) combined with no medication, NRT, bupropion or Champix on 4 week quit rates. The heading and bar chart were each asterisked to a footnote which cited the NHS Stop Smoking Services: Service and Monitoring Guidance 2009/10. Adjacent to the bar chart were three bullet points: two highlighted DoH guidance whilst the third read 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons between treatments across different settings. The 4 week quit rates have not been measured directly but have been extrapolated from longer term quit rates'. The claim 'Champix – An evidenced-based choice in smoking cessation' ran below the text described above followed by the prescribing information. The product logo appeared in the bottom right hand corner.

The Panel noted that the NHS Service and Monitoring Guidance stated that Champix had been proven to be a highly cost-effective treatment resulting in average success rates of 61% at 4 weeks in the first and second quarters of 2008/2009. All motivated quitters should be given the optimum chance of success in any quit attempt and NRT, Champix and bupropion should all be made available in combination with intensive behavioural support as first-line treatments (where clinically appropriate).

The Panel considered that although the heading 'NHS Stop Smoking Services:' appeared in a green font, the same shade as the Champix data in the bar chart, readers would not assume that the advertisement was the official NHS Guidance or that Champix was its medicine of choice as alleged. It was clearly an advertisement for Champix. It featured promotional claims and prescribing information. No breach of Clause 7.2 was ruled.

2 The bar chart showing 4 week quit rates

COMPLAINT

Johnson & Johnson noted that the bar chart was referenced to the NHS Stop Smoking Services: Services and monitoring Guidance 2009/10 and was titled 'The relative impact of a variety of evidence-

based stop smoking interventions and pharmacotherapies upon 4 week quit rates'. The heading of the bar chart clearly indicated that the data portrayed the 'relative impact' of stop smoking interventions. 'Relative' emphasised the intention to draw a direct comparison between the treatments presented. However, any such comparison would be meaningless as there was no indication as to whether the differences were statistically significant. In addition, there were no patient numbers presented in the bar chart. This meant that the reader could not judge the context of the data. Johnson & Johnson alleged that the bar chart was misleading.

Pfizer argued that the title of the bar chart had been reproduced accurately from the NHS Stop Smoking Guidance and that no claim of statistical significance had been made or implied. Johnson & Johnson disagreed. The fact that the title had been faithfully reproduced and that no statistics were available did not make it acceptable to present data which implied superiority of one treatment over another in a promotional item, where superiority had not been demonstrated or referenced. It was an established principle under the Code that where graphically presented data suggested superiority, it was assumed to be statistically significant unless otherwise specified. Johnson & Johnson alleged that the comparative bar chart was misleading and hence in breach of Clauses 7.2, 7.3 and 7.8.

RESPONSE

Pfizer submitted that the bar chart had been reproduced from the NHS Stop Smoking Guidance. The title of the bar chart in the advertisement took the wording directly from the original. In addition, Pfizer had added a description alongside the bar chart which stated that the authors used the Cochrane Database of systematic reviews of smoking cessation treatments and performed indirect comparisons between treatments. It was therefore clear to the reader that this was not an interventional clinical trial which made direct comparisons between treatments. As this was not a clinical trial with an a priori hypothesis being tested there was no statistical analysis. Pfizer had presented the data as reported by the NHS which was in the public domain. Reporting data from Cochrane systematic reviews of evidence was an important addition to reporting efficacy results from single trials. Pfizer had deliberately also referenced a body of clinical trial evidence for Champix (Nides *et al*, Gonzales *et al*, Jorenby *et al* and Aubin *et al*). The NHS report provided further supporting data to the clinical trial evidence, it was from a reputable source and of interest to health professionals who worked in smoking cessation. Pfizer had represented the data in an accurate, balanced, fair and objective manner, therefore, it denied breaches of Clauses 7.2, 7.3 and 7.8.

PANEL RULING

The Panel noted, as stated in a very small footnote beneath the bar chart, that it was adapted from the Cochrane database of systematic reviews. It had been reproduced from the NHS stop smoking services: Services and Monitoring Guidance 2009/10. The bar chart invited the reader to directly compare the 4 week quit rates of each medicine and no medication when used in combination with 3 different evidenced based interventions. Champix had the most favourable outcome with each intervention. Further details about the Cochrane analysis were given in the third bullet point.

The Panel noted that the supplementary information to Clause 7.8 stated that artwork from published studies must be faithfully reproduced except where modification was necessary to comply with the Code. Differences which did not reach statistical significance must not be presented in such a way as to mislead. The Panel considered that the bar chart implied that in relation to each intervention statistically significantly more smokers quit with Champix than with any other treatment regimen. That was not necessarily so. The statistical significance of the data was unknown. The bar chart was misleading in this regard. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

3 Extrapolation of four week data

COMPLAINT

Johnson & Johnson noted that the third bullet point read 'These data have been prepared by the authors of this guidance from the Cochrane Reviews by performing indirect comparisons between treatments across different settings. The 4 week quit rates have not been measured directly but have been extrapolated from longer term quit rates.'

The Cochrane Reviews upon which these data were based appraised studies with a 6 month data point. It was therefore unclear either from the material or the source reference, how the 4 week data were calculated and whether the method used had suitable scientific validity for inclusion within promotional material.

Pfizer had failed to explain the basis of this extrapolated data, other than to state that the authors were reputable and credible and hence it believed the data to be valid. Johnson & Johnson alleged that this was insufficient as Pfizer was unable to substantiate the exact methods used to extrapolate the four week data.

Johnson & Johnson alleged that the extrapolation of data to a 4 week comparison without clear explanation or substantiation was misleading. The basis for the 4 week data had not been made sufficiently clear. Therefore, the advertisement was misleading and in breach of Clause 7.2. In addition, the 4 week data was not available and therefore could not be substantiated in breach of Clause 7.4.

RESPONSE

Pfizer noted that the text in the third bullet point stated that 4 week quit rates were not measured directly, but were extrapolated from longer term quit rates. As stated by Johnson & Johnson, the Cochrane reviews upon which these data were based appraised studies with a 6 month data point. In the same way that short term data from studies could be extrapolated to longer term, with the caveat that long term data had not been directly measured, here the reverse methodology had been used. The Cochrane reviews used longer term data, and the authors of the NHS guidance had extrapolated to the short term (4 weeks). In order not to mislead, Pfizer had made it clear that the 4 week data was calculated from longer term data rather than directly measured. Four week data was cited because this was the time point that was currently directly measured and monitored by NHS Stop Smoking Services across the UK.

Pfizer submitted that this data was substantiated by the published NHS Guidance document and the Cochrane Database of Systematic Reviews. In the same way that a calculation in a published peer reviewed clinical paper could be referenced to the clinical paper, a calculation in published NHS guidance could be referenced to the guidance. Pfizer did not believe that it would be expected to ask the authors of the NHS guidance, all of whom were recognised experts in the field of smoking cessation, to substantiate their data.

Pfizer denied a breach of Clauses 7.2 or 7.4.

PANEL RULING

The Panel noted its rulings and comments above. The Panel had concerns about the data. The Panel considered that the third bullet point made it clear that the 4 week quit rates had been extrapolated from longer term quit rates based on indirect comparisons between treatments across different settings. The Panel did not have a copy of the Cochrane reviews. On the evidence before it the Panel did not consider that it was necessary to provide further information about the calculation of the 4 week quit rates in the advertisement as alleged. The basis of the data was clear. No breach of Clause 7.2 was ruled on this very narrow point.

The Panel agreed with Pfizer that it was not for the authors of the NHS guidance to substantiate their data. The Code required that companies must be able to substantiate information, claim or comparisons (Clause 7.3) and such data be provided on request from a health professional (Clause 7.4).

The data presented in Pfizer's advertisement had to be capable of substantiation. The authors of the NHS guidance had extrapolated long term data published in the Cochrane reviews to a 4 week time point. No details about the calculation and any assumptions made were published in the NHS guidance document.

The Panel considered the allegation that Pfizer was unable to substantiate the four week data. The Panel noted the supplementary information to Clause 7.2 listed 'statistical information' as an area where particular care should be taken. This stated, *inter alia*, 'Care must be taken to ensure that there is a sound statistical basis for all information, claims and comparisons in promotional material.' It continued 'Instances have occurred where claims have been based on published papers in which the arithmetic and/or statistical methodology was incorrect. Accordingly, before statistical information is included in promotional material it must have been subjected to statistical appraisal'. The Panel considered that Pfizer's position, that it did not believe it would be expected to ask the authors of the NHS guidance, all of whom were recognised experts in the field of smoking cessation, to substantiate their data was unacceptable. It was Pfizer's responsibility to ensure that it could substantiate all claims and data in its promotional material irrespective of the source of such data. Thus, in the Panel's view, Pfizer should have satisfied itself that the extrapolation of the 4 week quit rates from longer term quit data was capable of substantiation before using such data in promotional material. Pfizer had not provided any data or detail about this calculation and thus the Panel considered that Pfizer had not substantiated the calculation of the 4 week quit rates. A breach of Clause 7.4 was ruled.

Complaint received **25 August 2009**

Case completed **11 November 2009**

CASE AUTH/2265/9/09

CONSULTANT RESPIRATORY PHYSICIAN v ASTRAZENECA

Promotion of Symbicort

A consultant respiratory physician complained about the conduct of a former representative from AstraZeneca in relation to the promotion of Symbicort (formoterol and budesonide) for chronic obstructive pulmonary disease (COPD).

The complainant's name appeared on the front of a document entitled 'Effective treatment of Chronic Obstructive Pulmonary Disease The NHS Challenge' next to the AstraZeneca logo. The complainant alleged that this might give the impression that she had either written or endorsed the document. Unbeknown to the complainant the document had been forwarded electronically to the local formulary group and had also been discussed in various primary care committees. The complainant had not written the report or approved of its contents. AstraZeneca had not asked for permission to use her name in such a misleading way. The report was written by the representative for the complainant who had asked for evidence why she should change her prescribing practice for patients with COPD. There was no mention that the representative was the author nor that the report was produced for the complainant's information only.

The detailed response from AstraZeneca is given below.

The Panel noted that the complainant's name, job title and hospital appeared in the lower right hand corner whilst the AstraZeneca corporate logo appeared in the bottom left hand corner. Text along the bottom referred the reader to prescribing information on the final four pages of the document. The document discussed the regional prevalence and financial burden of COPD and the estimated cost savings if an alternative ICS/LABA (inhaled corticosteroid/long acting B2 agonist) combination prescribing strategy to that currently used was adopted.

The Panel noted from the complainant that she had met the representative when speaking at a local meeting and the representative had promoted a switch from Seretide to Symbicort for cost and efficacy reasons. The complainant had asked for supporting evidence. However as acknowledged by AstraZeneca and contrary to company policy, there was no evidence that the representative had explained the Symbicort Budget Impact Model (BIM) tool nor that the complainant had requested a hard copy report. Nonetheless the representative subsequently provided the complainant with a hard copy and stated that a copy was going to be provided to the respiratory health care facilitator in primary care. Professional commitments and absence prevented the complainant from looking at the hard copy or reading relevant email correspondence. The complainant accepted that she should have checked the document more carefully. AstraZeneca acknowledged that again, contrary to company policy, there was no evidence that the complainant consented to the subsequent dissemination of the document.

The Panel considered that the design and layout of the front page implied that the complainant had written or otherwise endorsed the document. This was certainly the impression given to the local respiratory lead who received a copy by email. This was unacceptable and misleading about the complainant's role; a breach of the Code was ruled as acknowledged by AstraZeneca. It implied endorsement which in the Panel's view was contrary to the conventions of the profession; a breach of the Code was ruled as acknowledged by AstraZeneca. The Panel noted that the document at issue was in the format approved for use by the company and there was nothing on the front cover to dispel the impression that the report was written or endorsed by the named individual. High standards had not been maintained in this regard. A breach of the Code was ruled.

The Panel was very concerned about the role of the representative. Company procedures had not been followed. High standards had not been maintained and a further breach of the Code was ruled in this regard.

The Panel noted that the document was not a reprint of a published document nor was the complainant quoted within. No breaches of the Code were thus ruled.

A consultant respiratory physician complained about the conduct of a former representative from AstraZeneca UK Limited in relation to the promotion of Symbicort (formoterol and budesonide) for chronic obstructive pulmonary disease (COPD).

COMPLAINT

The complainant stated that her name had appeared on the front of a document entitled 'Effective treatment of Chronic Obstructive Pulmonary Disease The NHS Challenge' next to the AstraZeneca logo which might give the impression that she had either written or had endorsed the document which was compiled by the former AstraZeneca representative. Unbeknown to the complainant the document had been forwarded electronically for discussion to the local formulary

group and had also been discussed in various primary care committees. The complainant had neither written the paper, nor approved of its contents and nor had AstraZeneca asked for her permission to use her name in such a misleading way. The report was written by the representative as the complainant had asked for evidence why she should change her prescribing practice for patients with COPD. The representative had suggested a switch from Seretide to Symbicort for cost and efficacy reasons but there was no mention on the title page or in the report that the representative was the author and the report was produced for the complainant's information only.

Without the complainant's knowledge or approval the document subsequently appeared to have been fairly widely distributed and from discussions with colleagues in primary and secondary care the complainant strongly suspected that the assumption of 'consultant approval' ultimately led to the document being forwarded for discussion to the local formulary group meeting. The complainant was very unhappy that her name had been abused in this way and thought that AstraZeneca had breached Clause 10 of the Code. From discussions with senior managers at AstraZeneca the complainant understood that the company acknowledged its mistake (and had apologised verbally for this) and would carry out its own investigation. AstraZeneca had offered to send the complainant a summary of its own investigation once it was completed. However the complainant would like to ensure that mechanisms were in place so that this did not happen again and that as much as possible the document was taken out of circulation.

The complainant subsequently provided further information.

The complainant stated that she very rarely saw medical representatives but did meet the representative in question before a local educational meeting about COPD for GPs and practice nurses sponsored by AstraZeneca in Spring 2009 to discuss the programme. During that meeting the representative tried to convince the complainant to change her prescribing practice for COPD patients (switch from Seretide to Symbicort for cost and efficacy reasons). The complainant was not convinced and asked the representative for supporting evidence. The complainant's subsequent talk at the meeting was about a few case studies of COPD patients and had nothing to do with any pharmacological treatment.

The complainant had no further contact with the representative until a chance meeting in the hospital some time in mid July. The representative handed the complainant a paper copy of the document at issue and mentioned that she was also going to give a copy to the respiratory health care facilitator in primary care. At that stage the complainant was not aware of any work regarding Symbicort/Seretide by the local community health and care partnership. This had not been discussed in the local respiratory partnership meeting – a quarterly meeting between primary and secondary care representatives to discuss respiratory issues. The complainant was in a rush and had no time to discuss the document. The complainant did not look at the document again until she was emailed by the local respiratory lead expressing his surprise that a document with her name and the AstraZeneca logo had been forwarded to the local formulary group for discussion.

The complainant was copied into the email from the respiratory health care facilitator in primary care forwarding the document to the lead GP and a community pharmacist which arrived after the complainant's three week summer break. The complainant unfortunately did not open the attachment and so remained unaware that the front cover of the document implied that she had written or endorsed it. However the complainant did not think that her failure to respond to this email with an enclosed document bearing her name only (unbeknown to her at that time) amounted to consent for its ongoing distribution and considered that this should have been discussed verbally with her beforehand. The complainant strongly suspected from discussions with pharmacy and medical colleagues that the assumption of 'consultant approval' ultimately led to the document being forwarded to the local formulary group and various primary care committees.

The complainant accepted that she should have checked the document more carefully in the first instance but she felt strongly that the front cover with the title of the document, her name, designation and place of work plus the AstraZeneca logo was very misleading. There was no mention in the document of its author and even if it was only supposed to have been for the complainant it should have clearly stated the author's name on the front cover and that it was provided to the complainant for information only with no possible implication that she was involved in the report.

The representative sent the electronic version out (which from discussion with AstraZeneca seemed to breach company policies) and this obviously opened the door to rapid dissemination. There was no mention in the representative's email that the report was to be treated confidentially and was not for further dissemination and, according to the respiratory health care facilitator in primary care, the representative knew that she was going to forward it to the lead GP and a community pharmacist. The representative also copied it to her successor and one other colleague (the complainant did not know what his position in the company was).

The complainant was obviously concerned that the electronic version had gone beyond the local region by now and there was probably little she

could do about it. AstraZeneca was carrying out an internal investigation and would send the complainant a copy within the next two weeks. It had acknowledged its mistake verbally and offered to self report to the Authority but the complainant had chosen to initiate a complaint herself.

The complainant would like to ensure that AstraZeneca would put procedures in place that similar documents were now clearly labelled regarding their authorship and she hoped that the document bearing her name was taken out of circulation as much as possible.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 7.2, 9.1 and 9.3 of the Code in addition to Clauses 10.2, 10.3 and 10.4. The complainant had referred to Clause 10 in general.

RESPONSE

AstraZeneca stated that it took the complainant's concerns extremely seriously and had therefore undertaken a prompt and thorough investigation to establish the facts and take any necessary corrective action.

The issues that had been raised all related to the Symbicort Budget Impact Model (BIM). The BIM was a promotional tool in the form of a spreadsheet that was used by representatives to demonstrate a health-economic argument for the use of Symbicort in either asthma or COPD. The tool contained input fields for the entry of local demographic and product usage data from which the health-economic claims were automatically generated by a pre-programmed algorithm. It was created and certified by AstraZeneca for use by representatives promoting Symbicort.

Representatives were trained to use their laptop to explain and present the tool to a health professional and, if requested by the health professional, the representative could generate and print out a single written summary report (entitled 'Effective treatment of Chronic Obstructive Pulmonary Disease' if the therapy area being discussed was COPD) that they handed over directly to that health professional. The representative could personalise the report by putting the recipient's name and details on the front page of the report.

AstraZeneca believed that the overall complaint related to two aspects of the printed summary report generated by the BIM; firstly the appearance on the front page of the complainant's name and secondly the manner of the subsequent use and dissemination of the report by AstraZeneca.

AstraZeneca reviewed all the relevant approval and training documentation for the BIM, interviewed relevant existing employees involved in the creation, approval and training of the BIM tool and contacted and interviewed the representative in question who had left the company before this complaint arose.

AstraZeneca's investigation established the following:

1 With regard to the information that appeared on the front page of the written summary report:

- The complainant did not write the summary report, nor did she contribute to or endorse the content in any way. In fact, she was not aware that her name appeared on the front page of this report when it was first handed to her by the representative.
- The front page of the summary report prepared for the complainant had her name printed on it without a clarification that she was the recipient and nor was there a clarification that it had actually been prepared by AstraZeneca or its representative. This unintentional lack of clarification and the positioning of the complainant's name on the front sheet of the report could misleading imply that the complainant was the author of the report.
- The Symbicort BIM tool had no facility for entering any details on the front sheet of the summary report other than the recipient's name, and institutional details. The representative could personalise the summary report by entering in the recipient's details and then print a hardcopy, which was then handed to the recipient. The representatives were trained to only send an electronic version of the summary report with the recipients' prior permission and head office authorization. In this isolated case, approval to send the summary report electronically was granted by head office which did not first check that prior written permission had been granted by the recipient.
- The front page of the summary report prepared for any recipient might misleadingly appear to ascribe to that recipient the views contained in the report. Although this was unintentional (the intention was merely to personalise the report), sufficient care had not been taken to avoid such an impression. Furthermore, such an impression constituted a misleading claim regarding the authorship of the summary report. Therefore AstraZeneca accepted that the summary report breached Clauses 10.4 and 7.2.

2 With regard to the manner of the use and dissemination of the report:

- There was no evidence that the representative clearly explained the nature of the Symbicort BIM tool to the complainant, nor that the complainant specifically requested a hard-copy summary report from it.
- There was no evidence that the complainant requested, or gave consent to the representative to share a copy of the summary report with any other NHS colleagues either in hard copy or electronically. Although the complainant was aware of the representative's intention to share

a copy with the respiratory health care facilitator in primary care (an NHS colleague with whom the representative had separately discussed the BIM) she at that stage had not had a chance to view the hard copy.
- The representative obtained permission from head office for the electronic dissemination of the summary report. This permission was, however, granted without the proper internal approval process as stated above.
- AstraZeneca accepted that the unfortunate misleading impression regarding authorship created by the front page of the summary report and the manner in which it had been disseminated without the informed consent of the complainant was in breach of Clause 9.3.

This was a genuine unintentional mistake with a hard copy containing the error on its front page given to the health practitioner. AstraZeneca responded immediately it knew of the error and instigated a full investigation with a formal explanation and apology, independent of a complaint to the Authority. All the actions taken had been consistent with a company keen to maintain high standards when a genuine error had been made. This was an isolated set of events and immediate steps had been taken to ensure this was not replicated and AstraZeneca therefore denied a breach of Clause 9.1.

The summary report was not a quotation from the complainant; therefore, AstraZeneca did not believe Clause 10.2 was applicable nor that the summary report was in breach of Clause 10.2.

The summary report was not a quotation taken from a public broadcast, private occasion, medical conference or symposium. Therefore AstraZeneca did not believe Clause 10.3 was applicable nor that the summary report was in breach of Clause 10.3.

In response to the complainant's initial direct complaint to AstraZeneca (and before receiving the complaint via the Authority), AstraZeneca conducted an urgent investigation and took the following immediate actions:

- All relevant representatives were told to stop using the Symbicort BIM tool and delete it from their laptops, with immediate effect.
- BIM tools and all other similar types of documents for all brands were reviewed to ensure similar issues did not exist.

In addition, action was being taken with the individual who authorised the electronic dissemination of the complainant's report and all representatives would be reminded of the Code and AstraZeneca requirements relating to the use of BIM tools.

With regard to the retrieval of copies of the summary report prepared for the complainant, AstraZeneca was only aware of the dissemination of one hard-copy (the copy given to the complainant herself). It was not possible for AstraZeneca to retrieve the email versions that had now been distributed within the NHS.

In conclusion, AstraZeneca had addressed this matter with the seriousness it fully warranted and had offered the complainant a written apology.

AstraZeneca was determined to understand all the learnings from this case, share them widely within the company and ensure that such an error did not occur again.

PANEL RULING

The Panel noted that the 20 page document was headed 'Effective Treatment of Chronic Obstructive Pulmonary Disease. The NHS challenge'. The complainant's name, job title and hospital appeared in the lower right hand corner whilst the AstraZeneca corporate logo appeared in the bottom left hand corner. Text along the bottom referred the reader to prescribing information on the final four pages of the document. The document discussed the regional prevalence and financial burden of COPD and the estimated cost savings if an alternative ICS/LABA (inhaled corticosteroid/long acting B2 agonist) combination prescribing strategy to that currently used was adopted.

The Panel noted from the complainant that she had met the representative when speaking at a local meeting and the representative had promoted a switch from Seretide to Symbicort for cost and efficacy reasons. The complainant had asked the representative for supporting evidence. However as acknowledged by AstraZeneca and contrary to company policy, there was no evidence that the representative had explained the Symbicort BIM tool nor that the complainant had requested a hard copy report. Nonetheless the representative subsequently provided the complainant with a hard copy and stated that a copy was going to be provided to the respiratory health care facilitator in primary care. Professional commitments and absence prevented the complainant from looking at the hard copy or reading relevant email correspondence. The complainant accepted that she should have checked the document more carefully. AstraZeneca acknowledged that again, contrary to company policy, there was no evidence that the complainant consented to the subsequent dissemination of the document.

The Panel considered that the design and layout of the front page implied that the complainant had written or otherwise endorsed the document. This was certainly the impression given to the local respiratory lead who received a copy by email. This was unacceptable and misleading about the complainant's role; a breach of Clause 7.2 was ruled as acknowledged by AstraZeneca. It implied endorsement which in the Panel's view was contrary to the conventions of the profession a breach of Clause 9.3 was ruled as acknowledged by AstraZeneca. The Panel noted that the

document at issue was in the format approved for use by the company and there was nothing on the front cover to dispel the impression that the report was written or endorsed by the named individual. High standards had not been maintained in this regard. A breach of Clause 9.1 was ruled.

The Panel was very concerned about the role of the representative. Company procedures had not been followed on the creation and dissemination of the material. High standards had not been maintained and a further breach of Clause 9.1 was ruled in this regard.

The Panel noted that the complainant had cited Clause 10 of the Code which referred to the provision of reprints and the use of quotations. The Authority had referred to Clauses 10.2, 10.3 and 10.4. The document was not a reprint of a published document nor was the complainant quoted within. No breach of Clauses 10.2, 10.3 and 10.4 was thus ruled.

Complaint received **10 September 2009**

Case completed **17 November 2009**

CASE AUTH/2267/9/09

SHIRE v PROCTER & GAMBLE

Promotion of Asacol

Shire complained about two leavepieces and a journal advertisement promoting Asacol (modified release mesalazine) issued by Procter & Gamble. Asacol was indicated for the treatment of mild to moderate acute exacerbation of ulcerative colitis and for the maintenance of remission thereof. Asacol was also indicated for the maintenance of remission in Crohn's ileocolitis. Mesalazine was a 5-aminosalicylate (5-ASA).

The detailed response from Procter & Gamble is given below.

Shire alleged that the strapline 'confidence in colitis' beneath the product logo without an equally prominent reference to Asacol's indication promoted Asacol beyond its indication and also overstated the clinical benefits.

Shire noted that there were a number of different types of colitis ie: amoebic, collagenous, common variable immunodeficiency, drug induced, haemorrhagic, infective, ischemic, lymphocytic, post-radiation, pseudomembranous and ulcerative.

During inter-company dialogue, Procter & Gamble relied on the prominence of the correct indication, ulcerative colitis, on the one-page leavepiece, experience of health professionals with the product and the incidence of ulcerative colitis in the UK compared to other forms of colitis. Shire disagreed with Procter & Gamble's assertion that the leavepiece referred to 'ulcerative colitis' anywhere on its face. The references to ulcerative colitis were in any event too far removed from the strapline and logo cluster as well as insufficiently large to qualify it due to the close proximity of this strapline with the Asacol product logo.

Shire also alleged that the word confidence in 'confidence in colitis' encouraged use outside the terms of the summary of product characteristics (SPC) and licensed indications (as explained above) and implied superlative, special performance of the product which Procter & Gamble had failed to substantiate.

The Panel noted that Asacol was indicated for the treatment of mild to moderate acute exacerbations of ulcerative colitis and for the maintenance of remission thereof. It could also be used for the maintenance of remission in Crohn's ileo-colitis. The Panel noted that the front page of the leavepiece was headed 'Examples of how to write a script for Asacol 800mg MR tablets' beneath which was a table of possible dosing regimens and examples of how the prescription would be written. Three regimens were given 'Maintenance of remission (1.6g/day)', 'Mild acute UC (2.4g/day)' and 'Moderate acute UC (4.8g/day)'. The only time the term 'ulcerative colitis' was used in full was in the indications section of the prescribing information on the reverse.

The Panel considered that promotional material must be clear about the relevant indication for the medicine. The reader's attention would be drawn to the strapline 'confidence in colitis' in the bottom right-hand corner of the page. It appeared that Asacol could be used in all types of colitis which was not so. The Panel considered that the strapline 'confidence in colitis' was inconsistent with the Asacol SPC as alleged. A breach of the Code was zruled.

The Panel did not consider that 'confidence' *per se* implied a special merit that had not been substantiated nor did it imply a superlative. Prescribers should expect to be able to prescribe any licensed medicine with confidence. No breach of the Code was ruled.

A journal advertisement featured the photograph of a commuter reading a broad sheet newspaper. The headline running across the front and back pages was 'Back to normal everyday life …' '… Sooner – Asacol 4.8g/day vs. mesalazine 2.4g/day'. A claim beneath the photograph read 'For moderately active UC Higher dosing 4.8g/day Asacol 800mg MR tablets for fast, effective relief from a flare-up. Great news'.

Shire alleged that the claims that Asacol's performance was 'Great news' and that it could return a patient's life 'back to normal' – ie the pre-ulcerative colitis state – were unsubstantiable.

Shire was concerned about the heading 'Back to normal everyday life … Sooner – Asacol 4.8g/day vs. mesalazine 2.4g/day'. Ulcerative colitis was a chronic condition; patients had cycles of remission and relapse. Many patients in remission still had some symptoms. Procter & Gamble had not quantified what was meant by 'normal'. Shire alleged that 'normal', particularly in the phrase 'back to normal' (emphasis added), implied the patient's life was returned to the pre-ulcerative colitis state which was clearly not so as maintenance medicine was still needed. Shire alleged that the claim '*Back to* normal everyday life …' was not balanced or fair, was ambiguous, could not be substantiated and was exaggerated.

Shire was also concerned that given the cyclical nature of remission and relapse occurring with ulcerative colitis, the claim that patients could be 'normal' again after taking Asacol was of poor taste, and did not maintain high standards.

Shire alleged that the superlative 'Great' in relation to Asacol was inappropriate. The reference to 'Great news' clearly referred to the claim 'Back to normal everyday life…' '…Sooner – Asacol 4.8/day …'. Procter & Gamble had not qualified 'Great' nor had it provided evidence to substantiate it.

The Panel noted that the headline read 'Back to normal everyday life…' '… Sooner …'. The advertisement showed a commuter reading his newspaper on a busy train. The Panel did not consider that the advertisement implied that Asacol would return patients to the pre-ulcerative colitis state. 'Normal' was used to describe 'life' and implied that, despite still having ulcerative colitis, a patient could resume everyday activities. The Panel did not consider that 'normal' would be read as describing the patient's disease state. In the Panel's view the claim was not unbalanced or unfair and it could be substantiated. The claim did not exaggerate the clinical efficacy of Asacol. The Panel did not consider that the claim was in poor taste or failed to maintain high standards. No breach was ruled.

With regard to the claim 'Great news' the Panel noted that it was not a superlative. Fast, effective relief from an ulcerative colitis flare up would be 'Great news'. Beneath this claim was the further claim that Asacol 4.8g/day provided relief from rectal bleeding and increased stool frequency 10 days faster (median time to symptom relief 19 days vs 29 days) than mesalazine 2.4g/day (Marion *et al* 2006). The Panel did not consider that the claim was exaggerated as alleged. No breach was ruled.

The Panel noted that the product logo incorporated the strapline 'confidence in colitis'. The product logo appeared in the bottom right-hand corner of the advertisement where it was most likely to attract the reader's attention. The Panel noted its ruling above. The claim 'confidence in colitis' would become associated with Asacol. 'Colitis', however, was a general term and required qualification for the precise disease state to be described. The Panel noted that the advertisement referred to 'moderately active UC' although again the only reference to 'ulcerative colitis' was in the prescribing information. However, the strapline, which was in larger font than the reference to UC, implied that Asacol could be used in all types of colitis and this was not so. The Panel considered that the strapline 'confidence in colitis' was inconsistent with the Asacol SPC as alleged. A breach of the Code was ruled.

The prescribing leavepiece highlighted the fact that oral mesalazine products were not interchangeable and thus should not be prescribed generically. Shire noted that the leavepiece incorporated the views of a named doctor only and Procter & Gamble had failed to substantiate all the claims made in such opinion by reference to either the opinion of the majority of health professionals or other prescribing guidance.

The doctor's opinion as stated in the leavepiece, read: 'Similar to certain other drugs, for example anti-convulsives, mesalazine should be prescribed by brand name. Until we get hard evidence that two different mesalazine formulations are therapeutically equivalent and have the same benefits and sites of action, I consider that patients should not be switched and are kept on their existing brand name mesalazine preparation'.

Shire alleged that the above was misleading in a promotional context as it was one health professional's opinion and Procter & Gamble had not substantiated all the claims within this quotation, in particular the statement that 'patients should not be switched and are kept on their existing brand name mesalazine preparation'. Procter & Gamble had not quoted a source that showed that this statement either represented all if not the majority of health professionals or provided prescribing guidance to justify the same. Shire noted that the MIMS February 2009 guidelines stated 'Different aminosalicylates and their various forms are not interchangeable and are designed to release active drug at different sites along the colon. They should be prescribed according to their mode and site of action and the brand name should always be specified'. The MIMS guidance did not, however, go on to state that switching from an existing prescription should be avoided. As the named doctor expressly acknowledged in his quotation, there was no data to substantiate this claim (that patients on Asacol should not be switched to other 5-ASAs).

The Panel noted that the quotation from the named doctor 'I consider that patients should not be switched and are kept on their existing brand name mesalazine preparation' was unqualified. It might well be the view of the doctor quoted but promotional material had to reflect the balance of the evidence. The other supporting documentation referred to the differences between the various preparations and the need to avoid unplanned substitution. However it might be necessary to change patients' therapy for clinical reasons. In this regard the Panel noted Procter & Gamble's submission that patients should not be switched between different oral mesalazine products *unless there were specific clinical reasons to do so.* This advice was not given. Thus the Panel considered that the quotation at issue was misleading as alleged. A breach of the Code was ruled.

Shire Pharmaceuticals Ltd complained about the promotion of Asacol (modified release mesalazine) by Procter & Gamble Pharmaceuticals UK, Limited. Asacol was indicated for the treatment of mild to moderate acute exacerbation of ulcerative colitis and for the maintenance of remission thereof. Asacol was also indicated for the maintenance of remission in Crohn's ileocolitis. Mesalazine was a 5-aminosalicylate (5-ASA).

There were three items at issue; an 800mg MR tablets dosing leavepiece (ref AS7709/56655); a

journal advertisement (ref AS7965/58698.02) and a prescribing leavepiece (ref AS7927/58854.04).

1 Dosing leavepiece (ref AS7709/56655)

COMPLAINT

Shire alleged that by using the strapline 'confidence in colitis' beneath the product logo without an equally prominent reference to Asacol's indication on this leavepiece, Procter & Gamble had not only promoted Asacol beyond its indication but had also overstated the clinical benefits by the use of 'confidence' in the logo cluster.

Shire noted that under the heading 'colitis' in the Oxford Textbook of Medicine (3rd edition) the following types were listed: amoebic, collagenous, common variable immunodeficiency, drug induced, haemorrhagic, infective, ischemic, lymphocytic, post-radiation, pseudomembranous and ulcerative.

During inter-company dialogue, Procter & Gamble relied on the prominence of the correct indication, ulcerative colitis, on the one-page leavepiece, experience of health professionals with the product and the incidence of ulcerative colitis in the UK compared to other forms of colitis. Shire disagreed with Procter & Gamble's assertion that the leavepiece referred to 'ulcerative colitis' anywhere on its face. The references to ulcerative colitis were in any event too far removed from the strapline and logo cluster as well as insufficiently large to qualify it due to the close proximity of this strapline with the Asacol product logo. In relation to Procter & Gamble's other points, the Code was clear that the promotion of a product had to be consistent with its summary of product characteristics (SPC), which this leavepiece was not, and it was an inadequate defence to rely on the experience of health professionals and the incidence of ulcerative colitis. It could not be assumed that all newly qualified health professionals would be familiar with the indication for Asacol 800mg MR tablets or the incidence of ulcerative colitis in the UK compared with other forms of colitis.

Shire also alleged that the use of the word confidence in 'confidence in colitis' encouraged use outside the terms of the SPC and licensed indications (as explained above) in a way which would not be rational. Furthermore, 'confidence' in close proximity to the Asacol product name in the logo cluster implied superlative, special performance of the product which Procter & Gamble had failed to substantiate. Shire alleged breaches of Clauses 3.2 and 7.10 of the Code.

RESPONSE

Procter & Gamble noted that the leavepiece was a single double-sided A5 sheet. The front page presented examples of how a clinician could write a prescription for Asacol 800mg MR tablets for various licensed indications within ulcerative colitis. The strapline 'confidence in colitis' appeared in the bottom right-hand corner directly beneath the product logo 'Asacol 800mg MR Tablets (mesalazine)'. Prescribing information was on the reverse.

Procter & Gamble fundamentally disagreed with Shire's alleged breaches of the Code as the strapline was only intended be read in the context of the whole leavepiece where specific licensed indications for Asacol within ulcerative colitis were mentioned and formed an integral part of the material.

Procter & Gamble submitted that the leavepiece clearly illustrated and described examples of possible dosing regimens for Asacol 800mg MR tablets. These were presented in a table which formed the core of the leavepiece. Here the licensed indications for Asacol were described ie maintenance of remission, treatment of mild and moderate acute UC. The strapline 'confidence in colitis', which appeared with much less prominence ie in the bottom right-hand corner of the leavepiece, was intended to be read in the context of all of the information presented.

Procter & Gamble noted that Clause 7.2 stated *inter alia*, that 'Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. Procter & Gamble firmly believed this was the case for the leavepiece in question, and in its entirety, any clinician receiving this, whether familiar with ulcerative colitis or newly qualified, would be able to make an informed decision as to whether Asacol was a suitable and appropriate treatment choice.

Procter & Gamble submitted that the leavepiece neither endorsed nor encouraged Asacol 800mg MR tablets to be prescribed outside of the product's licensed indications. The strapline, when read in the context of the leavepiece, could not be misinterpreted nor did it encourage use outside of the licensed indications.

By referring to 'colitis' in the context of the leavepiece and mesalazine, Procter & Gamble had followed a concept used by physicians and patients as evidenced by the term used in names of organisations, journals, etc, clearly referring to ulcerative colitis in their respective context eg National Association of Crohn's and Colitis (NACC), European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA), Journal of Crohn's and Colitis (JCC), European Crohn's and Colitis Organisation (ECCO).

Turning to the word 'confidence', Procter & Gamble submitted that this did not portray any special or superlative quality to Asacol 800mg MR Tablet. The impression given to health professionals was that they could be reasonably assured that the product was appropriate for their patient, within the specific indications, given the level of evidence and patient-years of exposure with the product. Again, this was part of a general statement to be read in the context of the leavepiece.

In summary, Procter & Gamble submitted that the strapline 'confidence in colitis', when read in the context of the leavepiece, which provided information consistent with the SPC for Asacol 800mg MR tablets, and, given the disease area and recognisable nature of the class of medicine (mesalazine), would not mislead and certainly did not promote Asacol outside of its licence.

Procter & Gamble therefore submitted that the leavepiece complied with Clauses 3.2 and 7.10.

PANEL RULING

The Panel noted that Asacol 800mg MR tablets were indicated for the treatment of mild to moderate acute exacerbations of ulcerative colitis and for the maintenance of remission thereof. It could also be used for the maintenance of remission in Crohn's ileo-colitis. The Panel noted that the front page of the leavepiece was headed 'Examples of how to write a script for Asacol 800mg MR tablets' beneath which was a table of possible dosing regimens and examples of how the prescription would be written. Three regimens were given 'Maintenance of remission (1.6g/day)', 'Mild acute UC (2.4g/day)' and 'Moderate acute UC (4.8g/day)'. The only time the term 'ulcerative colitis' was used in full was in the indications section of the prescribing information on the reverse.

The Panel considered that promotional material must be clear about the relevant indication for the medicine. The reader's attention would be drawn to the strapline 'confidence in colitis' in the bottom right-hand corner of the page. It appeared that Asacol could be used in all types of colitis which was not so. The Panel considered that the strapline 'confidence in colitis' was inconsistent with the particulars listed in the Asacol SPC as alleged. A breach of Clause 3.2 was ruled.

The Panel did not consider that use of 'confidence' *per se* implied a special merit that had not been substantiated as alleged nor did it imply a superlative. Prescribers should expect to be able to prescribe any licensed medicine with confidence. In that regard the Panel ruled no breach of Clause 7.10.

2 Journal advertisement (ref AS7965/58698.02)

This advertisement featured the photograph of a commuter reading a broad sheet newspaper. The headline running across the front and back pages of the newspaper was 'Back to normal everyday life …' '… Sooner – Asacol 4.8g/day vs. mesalazine 2.4g/day'. A claim beneath the photograph read 'For moderately active UC Higher dosing 4.8g/day Asacol 800mg MR tablets for fast, effective relief from a flare-up. Great news'.

COMPLAINT

Shire alleged that the claims that Asacol's performance was 'Great news' and that the product could return a patient's life 'back to normal' – ie the pre-ulcerative colitis state – were unsubstantiable. Shire also repeated its concerns raised in Point 1 above in relation to the strapline – 'confidence in colitis' used in close proximity to the product logo.

Shire was concerned about the heading 'Back to normal everyday life … Sooner – Asacol 4.8g/day vs. mesalazine 2.4g/day'. Ulcerative colitis was a chronic condition whereby patients had cycles of remission and relapse. Many patients in remission still exhibited some symptoms. Procter & Gamble had failed to quantify what was meant by 'normal'. Shire alleged that the use of the word 'normal' (in the absence of any qualification such as symptom control) and particularly in the phrase '**back to** normal' (emphasis added) implied the patient's life was returned to the pre-ulcerative colitis state when this was clearly not the case, for example maintenance medicine still needed to be taken. Shire therefore alleged that the claim 'Back to normal everyday life …' was not balanced or fair, was ambiguous, could not be substantiated and exaggerated the clinical properties of Asacol in breach of Clauses 7.2, 7.4 and 7.10.

Shire alleged that Procter & Gamble's response highlighted the exacerbation of troublesome symptoms which disrupted a patient's life and routine. The response stated that a patient with well controlled symptoms could enjoy a reasonably 'normal' everyday life and would be able to perform a 'normal everyday' activity such as commuting to work. Shire did not accept these arguments because Procter & Gamble had not qualified what it meant by a reasonably 'normal' everyday life in the advertisement and the above arguments did not adequately address the use of the term '**back to** normal' which implied the pre-ulcerative colitis state.

Shire was also concerned that given the cyclical nature of remission and relapse occurring with ulcerative colitis, the claim that patients could be 'normal' again after taking Asacol was of poor taste, and did not maintain high standards. Shire therefore alleged a breach of Clause 9.1.

Shire alleged that use of the superlative 'Great' in relation to Asacol was inappropriate. The reference to 'Great news' clearly referred to the claim 'Back to normal everyday life…' '…Sooner – Asacol 4.8/day …'. Therefore the claim 'Great news' was logically to be understood to refer back to Asacol. Procter & Gamble had not qualified what it meant by 'Great', nor had it provided evidence to substantiate 'Great'. Shire alleged a breach of Clause 7.10.

Shire noted that during inter-company dialogue, Procter & Gamble had claimed that it had not ascribed the claim 'Great news' to an aspect of Asacol *per se* and thus it was not a superlative. For the reasons set out above, Shire disagreed with Procter & Gamble's interpretation of 'Great news'. In the context of the advertisement 'Great news'

related to the 'Back to normal' headline. By stating that such a claim was 'Great', Procter & Gamble had implied that Asacol had additional or superlative merits that other mesalazine products were lacking. Therefore, Shire alleged a breach of Clause 7.10.

RESPONSE

Procter & Gamble noted that the advertisement featured a patient travelling on a busy commuter train whilst reading his newspaper. The claims 'Back to normal everyday life …' and '… Sooner – Asacol 4.8/day vs. mesalazine 2.4g/day' appeared as a headline on his newspaper. Directly underneath the visual was the text 'For moderately active UC'. Below this the following claims appeared 'Higher dosing 4.8g/day Asacol 800mg MR tablets for fast, effective relief from a flare up. Great news'. Further details about symptom relief (rectal bleeding and increased stool frequency) were then given. Shire alleged that Procter & Gamble had failed to qualify what was meant by 'normal' and in particular 'Back to normal'. Shire alleged that the claims in which these words/phrases were used could not be substantiated and exaggerated the clinical properties of Asacol 800mg MR.

Procter & Gamble submitted that the claim in question was 'Back to normal everyday life … Sooner …' which was different from just 'Back to normal' as referred by Shire. 'Normal', when read in the context of the entire claim, and the overall theme of the advertisement, was sufficiently qualified both visually and through the inclusion of further text. The overall impression created by the advertisement was of a patient with ulcerative colitis who was able to carry out a normal everyday activity such as commuting to work whilst reading a newspaper. Such an activity, as clinicians would appreciate, would pose great difficulty to a patient experiencing the troublesome symptoms of an ulcerative colitis flare, for example, frequent bowel movements and visits to the toilet. Indeed the concept of health related normality for patients with ulcerative colitis and Crohn's disease, was having the freedom to carry out everyday life activities (family, social and work related) without hassle, etc.

Procter & Gamble submitted that clinicians would not get the impression from the advertisement that Asacol would return patients to the pre-ulcerative colitis state as alleged by Shire. Instead the advertisement represented 'normal' in terms of an ulcerative colitis patient being able to go about their everyday life and participate in regular, normal everyday activities, such as commuting on a train. The advertisement did not imply that patients with moderately active ulcerative colitis would, or could, return to the non-disease state. Furthermore, Procter & Gamble stated that it would be surprised if a clinician would make this wrong assumption as ulcerative colitis was a chronic condition.

Procter & Gamble submitted that the use of the word 'normal' and the headline 'Back to normal everyday life …' '…Sooner …' in the full context of the advertisement did not breach Clauses 7.2, 7.4 and 7.10 as alleged by Shire.

Procter & Gamble also strongly disagreed that the advertisement was in poor taste or that high standards had not been maintained through the use of headline 'Back to normal everyday life …' '… Sooner…'. Procter & Gamble therefore denied a breach of Clause 9.1.

Procter & Gamble submitted that with regard to the strapline 'confidence in colitis', again this was part of a general statement only to be read in the context of the advertisement, where information, consistent with the SPC for Asacol, was presented ie the statement 'For moderately active UC' which appeared directly beneath the visual. Procter & Gamble referred to its response to Point 1 above.

The phrase 'Great news' appeared as part of the claim 'Higher dosing 4.8g/day Asacol 800mg MR tablets for fast, effective relief from a flare up. Great News', which appeared under the visual part of the advertisement. Procter & Gamble submitted that it related to the headline in the newspaper which read 'Back to normal everyday life …' '… Sooner …'. Clinicians and patients would agree that fast and effective relief from the debilitating symptoms associated with a moderately active flare of ulcerative colitis would be considered and welcomed as great news. The claim did not ascribe any special qualities to Asacol itself. Therefore, Procter & Gamble denied a breach of Clause 7.10.

PANEL RULING

The Panel noted that the headline read 'Back to normal everyday life…' '… Sooner …'. The advertisement showed a commuter reading his newspaper on a busy train. The Panel did not consider that the advertisement implied that Asacol would return patients to the pre-ulcerative colitis state. 'Normal' was used to describe 'life' and implied that, despite still having ulcerative colitis, a patient could resume everyday activities. The Panel did not consider that 'normal' would be read as describing the patient's disease state. In the Panel's view the claim was not unbalanced or unfair. No breach of Clause 7.2 was ruled. The Panel considered that the claim could be substantiated. No breach of Clause 7.3 was ruled. The claim did not exaggerate the clinical efficacy of Asacol. No breach of Clause 7.10 was ruled. The Panel did not consider that the claim was in poor taste or failed to maintain high standards. No breach of Clause 9.1 was ruled.

With regard to the claim 'Great news' the Panel noted that it was not a superlative. Fast, effective relief from an ulcerative colitis flare up would be 'Great news'. Beneath this claim was the further claim that Asacol 4.8g/day provided relief from rectal bleeding and increased stool frequency 10 days faster (median time to symptom relief 19 days vs 29 days) than mesalazine 2.4g/day (Marion *et al* 2006). The Panel did not consider that the claim was

exaggerated as alleged. No breach of Clause 7.10 was ruled.

The Panel noted that the product logo incorporated the strapline 'confidence in colitis'. The product logo appeared in the bottom right-hand corner of the advertisement where it was most likely to attract the reader's attention. The Panel noted its ruling in point 1 above. The claim 'confidence in colitis' would become associated with Asacol. 'Colitis', however, was a general term and required qualification for the precise disease state to be described. The Panel noted that the advertisement referred to 'moderately active UC' although again the only reference to 'ulcerative colitis' was in the prescribing information. However, the strapline, which was in larger font than the reference to UC, implied that Asacol could be used in all types of colitis and this was not so. The Panel considered that the strapline 'confidence in colitis' was inconsistent with the particulars listed in the Asacol 800mg MR SPC as alleged. A breach of Clause 3.2 was ruled.

3 Prescribing leavepiece (ref AS7927/58854.04)

The leavepiece highlighted the fact that oral mesalazine products were not interchangeable and thus should not be prescribed generically.

COMPLAINT

Shire noted that the leavepiece incorporated the views of a named doctor only and Procter & Gamble had failed to substantiate all the claims made in such opinion by reference to either the opinion of the majority of health professionals or other prescribing guidance.

Shire noted that the doctor's opinion as stated in the leavepiece, read:

'Similar to certain other drugs, for example anti-convulsives, mesalazine should be prescribed by brand name. Until we get hard evidence that two different mesalazine formulations are therapeutically equivalent and have the same benefits and sites of action, I consider that patients should not be switched and are kept on their existing brand name mesalazine preparation.'

Shire alleged that the above was misleading in a promotional context as it was the opinion of one health professional and Procter & Gamble had not substantiated all the claims within this quotation, in particular the statement that 'patients should not be switched and are kept on their existing brand name mesalazine preparation'. Procter & Gamble had not quoted a source that showed that this statement either represented all if not the majority of health professionals or provided prescribing guidance to justify the same. Shire noted that the MIMS February 2009 guidelines stated 'Different aminosalicylates and their various forms are not interchangeable and are designed to release active drug at different sites along the colon. They should be prescribed according to their mode and site of action and the brand name should always be specified'. The MIMS guidance did not, however, go on to state that switching from an existing prescription should be avoided. As the named doctor expressly acknowledged in his quotation, there was no data to substantiate this claim (that patients on Asacol should not be switched to other 5-ASAs). For the above reasons, Shire alleged a breach of Clause 7.2.

Shire alleged that Procter & Gamble's response during inter-company dialogue was to state that the opinion was current and consistent with the prescribing guidance for mesalazines. However Procter & Gamble's correspondence did not provide details of any prescribing guidance to support the claim. Shire thus did not accept Procter & Gamble's position.

RESPONSE

Procter & Gamble noted that the title of the leavepiece, 'When prescribing oral mesalazine Are you confident that your patients are receiving the therapy that their Gastroenterologist intended?', appeared above a visual of a patient receiving their prescription in the pharmacy. The heading on the second page stated '5-ASAs are not interchangeable'. The subheading stated that 'Oral mesalazine is one of the few therapeutic classes where brand name prescribing is recommended'. Shire had alleged that use of this clinical opinion in the material was misleading in breach of Clause 7.2.

Procter & Gamble submitted that the focus of the leavepiece was the non-interchangeability of all oral mesalazine products and not switching between products, as alleged by Shire. In the context of oral mesalazine products, due to their individual release characteristics, non-interchangeability between different brands was widely agreed, documented and supported. In order to support the non-interchangeability of oral mesalazine products the leavepiece referred to MIMS (February 2009 [when the material was prepared], and was consistent with current MIMS September 2009 and BNF March 2009) and a clinical opinion from a named doctor, and cited two other references, Forbes and Chadwick (1997) and Forbes *et al* (2005).

Procter & Gamble submitted that the leavepiece also stated that 'Asacol 800 mg MR tablets and Asacol 400 mg MR tablets: are not interchangeable (consistent with prescribing other 5-ASAs)'. The quotation and non-interchangeability statements applied to all other oral mesalazine products. Indeed, patients should not be switched between different oral mesalazine products unless there were specific clinical reasons to do so. Therefore, the opinion in its entirety supported the fact that *switching* between oral mesalazine products should not be considered due to the nature of the non-interchangeability between such products. Procter & Gamble denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the quotation from the named doctor 'I consider that patients should not be switched and are kept on their existing brand name mesalazine preparation' was unqualified. It might well be the view of the doctor quoted but promotional material had to reflect the balance of the evidence. The other supporting documentation referred to the differences between the various preparations and the need to avoid unplanned substitution. However it might be necessary to change patients' therapy for clinical reasons. In this regard the Panel noted Procter & Gamble's submission that patients should not be switched between different oral mesalazine products *unless there were specific clinical reasons to do so*. This advice was not given. Thus the Panel considered that the quotation at issue was misleading as alleged. The Panel ruled a breach of Clause 7.2.

Complaint received **15 September 2009**

Case completed **4 November 2009**

CASE AUTH/2270/10/09

ALLERGAN v MERZ PHARMA

Promotion of Xeomin

Allergan complained about the promotion of Xeomin (botulinum neurotoxin type A) by Merz Pharma. The claim at issue 'At least as effective as Botox with a similar safety profile' was referenced to Benecke *et al* (2005) and Roggenkamper *et al* (2006) and appeared on an exhibition panel at the Association of British Neurologists meeting in Liverpool in June 2009. Allergan marketed Botox (botulinum neurotoxin).

Allergan alleged that the use of the unqualified claim 'At least as effective as' when based on the results from two non-inferiority studies did not accurately reflect the available evidence and was misleading. A non-inferiority trial was only intended to show that the effect of a new treatment was not worse than that of an active control by more than a specified margin. Therefore, it was possible to claim that Xeomin was no worse than Botox by the pre-specified margins in the studies.

Allergan agreed it was true that a product that had been shown to be non-inferior to another product might be equivalent to it, or even superior. However, without evidence supporting equivalence or superiority, all that could be said on the basis of a non-inferiority study was that the product was no worse than the comparator by the pre-specified margins.

In order to make the claim 'At least as effective as', further evidence that confirmed equivalent efficacy and clinically relevant superiority would be required. A clinician was likely to interpret the claim at issue as meaning this evidence existed, which it did not.

The detailed response from Merz is given below.

The Panel considered that there was a difference between showing non-inferiority to showing comparability. The Panel considered on the basis of the data the claim that Xeomin was 'At least as effective as Botox' did not reflect the available evidence. It implied possible superiority of Xeomin as alleged and was misleading. Breaches of the Code were ruled.

Upon appeal by Merz the Appeal Board noted that both parties agreed that Benecke *et al* and Roggenkamper *et al* were non-inferiority studies that showed that Xeomin was no worse than Botox by a pre-specified margin (delta) that was clinically acceptable.

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

Allergan Ltd complained about the promotion of Xeomin (botulinum neurotoxin type A) by Merz Pharma UK Ltd. The claim at issue 'At least as effective as Botox with a similar safety profile' was referenced to Benecke *et al* (2005) and Roggenkamper *et al* (2006) and appeared on an exhibition panel at the Association of British Neurologists meeting in Liverpool in June 2009.

Allergan marketed Botox (botulinum neurotoxin).

COMPLAINT

Allergan alleged that the use of the unqualified claim 'At least as effective as' when based on the results from two non-inferiority studies did not accurately reflect the available evidence and was misleading. A non-inferiority trial was only intended to show that the effect of a new treatment was not worse than that of an active control by more than a specified margin. Therefore, from Roggenkamper *et al* it was possible to claim that Xeomin was no worse than Botox by the pre-specified margin in the Jankovi Rating Scale (JRS) sum score. From Benecke *et al* it was possible to claim that Xeomin was no worse than Botox by the pre-specified margin in the Toronto Western Spasmodic Torticollis Scale (TWSTRS) severity score.

Allergan agreed it was true that a product that had been shown to be non-inferior to another product might be equivalent to it, or even superior. However, without evidence supporting equivalence or superiority, all that could be said on the basis of a non-inferiority study was that the product was no worse than the comparator by the pre-specified margin. The European Medicines Evaluation Agency (EMEA) Guideline on the Choice of the Non-inferiority Margin (EMEA/CPMA/EWP/2158/99) summarised it as:

'The objective of a non-inferiority trial is sometimes stated as being to demonstrate that the test product is not inferior to the comparator. However, only a superiority trial can demonstrate this. In fact a non-inferiority trial aims to demonstrate that the test product is not worse than the comparator by more than a pre-specified, small amount. This amount is knows as the non-inferiority margin, or delta'.

To make the claim 'At least as effective as', further evidence confirming equivalent efficacy and clinically relevant superiority would be required. A clinician was likely to interpret the claim at issue as meaning this evidence existed, which it did not.

Allergan alleged that the claim 'At least as effective as Botox with a similar side effect profile' without appropriate context and qualification was in breach of Clauses 7.2 and 7.3 of the Code. This claim would be interpreted to mean not only equivalence but also possible superior efficacy, and this data was not available.

RESPONSE

Merz submitted that the claim 'At least as effective as Botox' complied with the Code, however, Allergan had not previously mentioned an allegation of a breach of Clause 7.3 or that the claim might be misleading. Merz therefore did not believe that the requirement for inter-company dialogue had been fulfilled in these regards. Equally, the part of the claim on the safety profile had not been explored between the companies or raised as an issue by Allergan.

The two studies in question (Benecke *et al* and Roggenkamper *et al*) were used as part of the regulatory submission for the Xeomin marketing authorization and as such the methodology and the 'non-inferiority margin' had been accepted by European and other regulators.

The Xeomin claim 'At least as effective as Botox' was internally approved following thorough research into its appropriateness especially with reference to non-inferiority studies.

Firstly, Merz reviewed previous cases. Only one case in which the Panel commented on the interpretation of a non-inferiority trial was found involving this specific wording. In Case AUTH/1667/12/04: a clinical trial was cited where Cancidas was shown to be non-inferior to AmBisome. The Panel commented twice upon this non-inferiority clinical trial. It was clear that the Panel's views of non-inferiority results was 'at least as effective as'. This was an important factor in approving this claim.

Secondly, a literature search was conducted to ascertain the statisticians' view of the non-inferiority result. An article published as an extension to the CONSORT (Consolidated Standards of Reporting Trials) statement published in JAMA (Piaggio *et al*, 2006) stated 'Non-inferiority trials are intended to show whether a new treatment has at least as much efficacy as the standard or is worse by an amount less than [delta]'. With respect to the delta it stated 'A prestated margin of n is often chosen as the smallest value that would be a clinically important effect'.

Thus, if the difference between the two products, defined by the confidence interval, was less than the 'delta' (or non-inferiority margin) the difference between the products was clinically unimportant. The products could then be described as 'non-inferior' or 'no worse than' each other. This therefore left only two possibilities that the new treatment (in this case Xeomin) was as good as or better than the comparator (Botox). That was to say it was 'at least as good as' Botox.

As it was an established principle of the Code that all claims referred to the clinical situation, to suggest that Xeomin might be inferior to Botox by an amount that was not clinically relevant would be misleading. As a difference less than this 'delta' would be clinically unimportant it could be stated that, clinically, Xeomin had at least as much efficacy as Botox (by adapting the CONSORT statement above).

The EMEA guideline stated that the 'delta' was chosen '…to show that there is no important loss of efficacy if the test product is used instead of the reference'. It was later stated that this was 'supported by evidence of what is considered an unimportant difference in the particular disease area'.

The EMEA guideline further proved that the delta was clinically unimportant reinforcing the message that Xeomin was no worse than Botox leaving only that it may be the same or better – or at least as good as – Botox.

Allergan's allegation that equivalence and possible superiority were not proven by a non-inferiority trial was directly contradicted by Laster and Johnson (2003) who stated that 'The terminology 'at least as good as' or equivalently, non-inferiority, may be interpreted as either literal equivalence or superiority'. This peer reviewed paper in a statistics journal was at odds with Allergan's view. It seemed rational to accept the peer reviewed paper authors' view as they did not have a vested interest in a particular viewpoint, unlike the unreferenced statement from Allergan. Whilst Merz had no interest in promoting 'equivalence' or 'superiority' for Xeomin over Botox without specific evidence of such, this paper clearly demonstrated that Allergan's arguments were fundamentally flawed.

Merz submitted that the published evidence fully supported the claim 'At least as [good] as Botox'. Merz was firmly convinced that directly employing words previously used by the Panel in describing the exact same type of study meant that the claim could not be in breach of Clause 7.2.

PANEL RULING

The Panel noted Merz's comments that Allergan had not alleged that the claim was misleading in inter-company dialogue and therefore that aspect of the complaint should not proceed. The Panel noted that in inter-company dialogue Allergan had referred to Clause 7.2 which included a requirement that material should not mislead. Clause 7.3 also

included a requirement that comparisons should not be misleading. Whilst good practice it was not necessary to cite each clause at issue in inter-company dialogue. The substance of the complaint should be clearly identified and discussed and the clauses subsequently cited relevant to that discussion. Therefore the Director decided that in the circumstances the Panel could consider the alleged breach of Clause 7.3.

The Panel noted that both parties agreed that Benecke *et al* and Roggenkamper *et al* were non-inferiority studies. It was also agreed that Xeomin could be described as no worse than Botox. The Panel considered that there was a difference between showing non-inferiority to showing comparability. The Panel considered on the basis of the data the claim that Xeomin was 'At least as effective as Botox' did not reflect the available evidence. It implied possible superiority of Xeomin as alleged and was misleading. A breach of Clauses 7.2 and 7.3 was ruled.

APPEAL BY MERZ

Merz submitted that the claim 'At least as effective as Botox' complied with the Code based upon case precedent including wording used directly by the Panel, peer reviewed statistical publications and an EMEA guideline. In its ruling the Panel accepted that Xeomin was no worse than Botox. However the Panel also stated that the two studies could not be used to state that the two products were comparable and that the claim 'At least as effective as Botox' implied possible superiority and that this was misleading. The Panel had not commented in its ruling on Merz's defense of the claim, despite quoting Allergan's allegation in full. This disadvantaged Merz in its appeal.

Previous case precedent

Merz submitted that the Panel had previously ruled positively on the description of a 'non- inferiority' trial in Case AUTH/1667/12/04, in which the claim used was 'Cancidas is at least as effective as Ambisome …'. In the clinical trial in question Cancidas was shown to be non-inferior to AmBisome. The complaint was specifically 'Although the bullet point following the claim stated that 'Cancidas was at least as effective as Ambisome …' the reader was left with the distinct impression that Cancidas was better than Ambisome'. This was essentially the identical claim at issue in Case AUTH/2270/10/09. In its ruling the Panel had commented twice upon this non-inferiority clinical trial. The quotations were 'The Panel considered that the claim implied that Cancidas was an alternative first line antifungal therapy to Ambisome and noted the two prominent bullet points set out the reasons why that was so, ie **the two were at least as effective as each other** but Cancidas was significantly better tolerated', the Panel went on to state it '**did not accept that the claim […] implied greater efficacy for Cancidas** …' and 'The claim summarized the data which had already been presented [that the study showed non-inferiority with respect to efficacy but better tolerability] ie that Cancidas **was at least as effective as** Ambisome but better tolerated' (emphasis added by Merz).

Merz noted that the Panel ruled no breach of Clause 7.2 and that it was clear that the Panel's view of non-inferiority results was 'at least as effective as'. This was an important factor in approving this claim.

Merz noted that the Panel in the current case (Case AUTH/2270/10/09) had ruled that the claim at issue had 'implied superiority' and that this was misleading. This contradicted its previous position (as in the first quotation above) where the Panel stated that it 'did not accept that the claim implied greater efficacy …'. Merz was surprised and concerned that the ruling did not include an explanation as to why the Panel had gone against this precedent. It would be a disturbing precedent itself if previous Panel rulings and wording used by the Panel could not be used with assurance by companies to approve material. It would question the rationale of publishing the case reports and go against the principle of natural justice where each company would be treated equitably.

Appropriate use of statistical terminology

Merz noted that it had submitted two statistical papers published in peer reviewed journals and further information from the EMEA guideline partially quoted by Allergan. The first paper was an extension to the CONSORT statement published in JAMA (Piaggio *et al*) which stated that 'Non-inferiority trials are intended to show whether a new treatment has at least as much efficacy as the standard or is worse by an amount less than [delta]'. With respect to the delta it stated that 'A prestated margin of noninferiority is often chosen as the smallest value that would be a clinically important effect'.

Thus, Merz submitted that if the difference between the two products, defined by the confidence interval, was less than the 'delta' (or non-inferiority margin) the difference between the products was clinically unimportant. The products could then be described as 'non-inferior' or 'no worse than' each other. This therefore left only two possibilities that the new treatment (in this case Xeomin) was as good as or better than the comparator (Botox) ie it was 'at least as good as' Botox.

Merz submitted that as it was an established principle of the Code that all claims referred to the clinical situation; to suggest that Xeomin might be inferior to Botox by an amount that was not clinically relevant would be misleading. As a difference less that this 'delta' would be clinically unimportant it could be stated that, clinically, Xeomin had at least as much efficacy as Botox (by adapting the CONSORT statement above).
Merz submitted that Laster and Johnson refuted Allergan's allegation, and went against the Panel

ruling, that equivalence and possible superiority were not proven by a non-inferiority trial. This paper stated that 'The terminology "at least as good as" or equivalently, non-inferiority, may be interpreted as either literal equivalence or superiority'. It seemed rational to accept the peer reviewed paper authors' view as they did not have a vested interest in a particular viewpoint, unlike Allergan's unreferenced statement. Whilst Merz had no interest in promoting 'equivalence' or 'superiority' for Xeomin over Botox without specific evidence of such, this paper clearly demonstrated that Allergan's arguments and the Panel's ruling were fundamentally flawed.

Merz submitted that the statement provided by Allergan from the EMEA guideline was a direct 'cut and paste' however it represented a narrow view of that guideline and failed to capture the full context of the document with respect to the clinical situation. The guideline went on to state that the 'delta' was chosen '…to show that there is no important loss of efficacy if the test product is used instead of the reference' and that this was 'supported by evidence of what is considered an unimportant difference in the particular disease area'.

Merz submitted that the EMEA guideline quoted by Allergan further established that the delta was clinically unimportant reinforcing the message that Xeomin was no worse than Botox leaving only that it might be the same or better – or at least as good as – Botox. Merz submitted that the published evidence fully supported the claim 'At least as effective as Botox'. The Panel's ruling of a breach of Clauses 7.2 and 7.3 should be overturned as:

- it directly contradicted a previous ruling for these types of trials thus going against the principles of precedent and natural justice;
- it went against the only two peer reviewed published papers on the subject of 'non-inferiority' trials and;
- contradicted the Code principle that claims referred to the clinical situation by narrowly interpreting a short section of an EMEA guideline out of context and without reference to its clinical relevance.

RESPONSE FROM ALLERGAN

Allergan was surprised by Merz's stance in this case and its appeal of the Panel's ruling. Allergan disagreed that Merz had been disadvantaged in any way. The claim at issue 'At least as effective as Botox with a similar side effect profile' was not supported by case precedent, or peer reviewed publications, as suggested by Merz.

Allergan stated that in essence the matter was very simple. There was a single claim at issue which was on a promotional stand at the Association of British Neurologists meeting in June 2009. Allergan understood from inter-company correspondence that this claim was also included in other Xeomin promotional materials. Allergan alleged the use of the unqualified claim 'At least as effective as', based on the results from two non-inferiority studies, did not accurately reflect the available evidence and was misleading. Without appropriate context and qualification readers would interpret the claim to mean equivalence but also possible superior efficacy, and this data was not available. A non-inferiority trial was only intended to show that the effect of a new treatment was not worse than that of an active control by more than a specified margin. Therefore, from Roggenkamper *et al* it was possible to claim that Xeomin was no worse than Botox by the pre-specified margin in the JRS sum score and from Benecke *et al* it was possible to claim that Xeomin was no worse than Botox by the pre-specified margin in the TWSTRS score. It was true that a product that had been shown to be non-inferior to another product might actually be equivalent to it, or even superior. However, without evidence supporting equivalence or superiority, all that could be said on the basis of a non-inferiority study was that the product was not worse than the comparator by the pre-specified margin in the study.

Case precedent

Allergan disagreed with Merz's interpretation of Case AUTH/1667/12/04 that the Panel found that use of a non-inferiority study supported the claim that Cancidas was 'at least as effective as' Ambisone. The claim upon which the Panel had ruled was a different one - whether Cancidas could be used as an alternative to Ambisone. The Panel considered that the supporting evidence, of which the non-inferiority study was only a part, did support this claim. The Panel was not asked to rule on, and did not comment on, whether the claim 'at least as effective as' could be made based on a non-inferiority study. Therefore, Allergan strongly disagreed with Merz's conclusion that the Panel had gone against a previous case precedent and was very concerned by Merz's suggestion that it was not being treated equitably.

Allergan alleged that there was a much more relevant case, Case AUTH/2131/6/08, in which the Panel ruled that the claims 'Versatis is comparable to pregabalin in reducing pain intensity at 4 weeks' and 'Statistically shown to be at least comparable in efficacy to pregabalin' were not supported by a non-inferiority study. The Panel clearly stated in its ruling that it 'considered there was a difference between showing non-inferiority to showing comparability'. Whilst case precedent was a helpful guide each case must be ruled on its own merits.

Appropriate use of statistical terminology

Whilst there had been significant discussion around statistical terminology, it was important to remember the context of the claim. It was a stand alone, unqualified claim, on an exhibition panel. Allergan alleged that the claim 'At least as effective as Botox with a similar side effect profile' without

appropriate context and qualification would be interpreted to mean equivalence but also possible superior efficacy. Data to support equivalence or superiority was not available. Merz had referenced to two statistical papers and further information from the EMEA guideline provided by Allergan.

Regarding Piaggio *et al*, Allergan disagreed with Merz's 'adaptation' of the section quoted from the CONSORT statement. If products could be described as 'non-inferior' or 'no worse than' each other it did not follow that there were only two possibilities as suggested by Merz – that the new product (Xeomin) was (1) as good as or (2) better than the comparator (Botox). The new product could be worse than the comparator but by less than the delta. Whilst Merz alleged it would be 'misleading' to suggest that Xeomin might be inferior to Botox by an amount less than the delta, it was equally misleading to suggest that Xeomin might be superior (better than) Botox.

With regard to Laster and Johnson, Allergan noted that it was interesting to read beyond the limited quotation provided by Merz. 'The terminology "at least as good as" or equivalently, non-inferiority, may be interpreted as literal equivalence or superiority. Since the statistical demonstration of literal equivalence is fruitless (that is, proving the null hypothesis of no difference), an operational definition must be considered which allows experimental therapy to be inferior to standard therapy by a clinically tolerable amount'. Therefore, this paper seemed to support the view that a non-inferiority trial allowed experimental therapy to be 'inferior to standard therapy by a clinically tolerable amount', not just 'as good as' or 'better'. With reference to the EMEA guideline on the choice of the non-inferiority margin, the additional sections selected by Merz had not supported its case for the use of the claim 'At least as effective as'. The guideline clearly stated that 'The objective of a non-inferiority trial is sometimes stated as being to demonstrate that the test product is not inferior to the comparator. However, only a superiority trial can demonstrate this. In fact a non-inferiority trial aims to demonstrate that the test product is not worse than the comparator by more than a pre-specified, small amount. This amount is known as the non-inferiority margin, or delta'. In order to claim 'At least as effective as', further evidence that confirmed equivalent efficacy and clinically relevant superiority would be required. A clinician was likely to interpret the claim at issue as meaning this evidence existed, which it did not.

Allergan disagreed with Merz's interpretation of case precedent and published evidence. Allergan did not believe it had been selective or narrow in its interpretation of the EMEA guideline presented. Whilst there had been significant discussion around statistical terminology, it was important to remember the context of this claim and how it would be interpreted by the reader.
Therefore, as previously stated, Allergan alleged that the claim 'At least as effective as Botox with a similar side effect profile' without appropriate context and qualification was in breach of Clauses 7.2 and 7.3 of the Code. The claim would be interpreted to mean equivalence but also possible superior efficacy, and this data was not available.

APPEAL BOARD RULING

The Appeal Board noted that both parties agreed that Benecke *et al* and Roggenkamper *et al* were non-inferiority studies that showed that Xeomin was no worse than Botox by a pre-specified margin (delta) that was clinically acceptable.

The Appeal Board noted that Merz had cited Case AUTH/1667/12/04 in support of the use of the claim at issue because it submitted that in that case the Panel had ruled that the claim 'Cancidas was at least as effective as AmBisome' was acceptable based upon a non-inferiority trial. However, the Appeal Board noted that this claim had appeared as a bullet point in support of the actual claim at issue which was about the use of Cancidas instead of AmBisome as first line empirical treatment. The Panel had not been called upon to consider the claim '…at least as effective as …' *per se*. In any event each case was judged on its merits. The context in which claims were used was important. The Appeal Board was concerned that Merz had selected a part of the Panel ruling in Case AUTH/1667/12/04 to support its case.

The Appeal Board noted that non-inferiority studies showed that even if one product was worse than another it was only worse within clinically unimportant limits. The Appeal Board noted Merz's submission at the appeal that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's view the claim 'At least as effective' not only implied equivalence but also possible superiority which was misleading. The Appeal Board did not consider that the claim could be substantiated by the available data. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3. The appeal was unsuccessful.

Complaint received **5 October 2009**

Case completed **4 January 2010**

CASE AUTH/2274/10/09

CONSULTANT NEUROLOGIST v ALLERGAN

Marketing survey

A consultant neurologist complained about a survey headed 'Neurology Pharmaceutical Survey' sent by a market research agency which consisted of two pages of 22 questions and sub-questions. Nine questions, ie all but one, on page 2 related to the use of botulinum toxin injections. Six of the questions specifically referred to the use of botulinum toxin injections for the treatment of primary headache or migraine.

The accompanying letter from the agency described the survey as a marketing study on the management of primary headache and migraine conditions. It was being carried out on behalf of a pharmaceutical company which had a specific interest in individual clinicians' treatment practice in this therapy area. The letter further stated that as this was a marketing study as opposed to a market research study participants would be identifiable to the company commissioning the research. A cheque for £35 was included.

The identity of the commissioning pharmaceutical company was not clear from the documentation. The agency confirmed that it was Allergan. Allergan marketed Botox (botulinum toxin). Botox was not licensed for the treatment of primary headache or migraine.

The complainant provided a copy of the material at issue, together with part of a poster of the more successful trial presented at the recent International Headache Society (IHS) meeting in Philadelphia (Dodick *et al* 2009). The complainant found it hard to believe that 'marketing study' was not a means of assembling large numbers of willing users of the medicine before the National Institute for Health and Clinical Excellence (NICE) had established whether the modest (though mathematically significant) improvement over the effect of placebo was cost-effective.

The complainant queried whether Allergan (through its agent) had strayed over the boundaries of honest promotion.

The detailed response from Allergan is given below.

The Panel noted Allergan's submission that the purpose of the survey was to seek information and opinion from senior health professionals actively involved in the management of primary headache and migraine. The information gained would ensure that Allergan's communications were effectively targeted. Allergan did not argue that the survey was market research outside the scope of the Code but described it as a marketing survey as the participants would be identified to the company. Allergan had examined the survey in relation to the requirements of the Code as non promotional material.

The Panel noted that most of the questions on page 2 of the survey referred to the use of botulinum toxin injections. Six of the questions referred to the use of such injections for the treatment of primary headache or migraine. One question asked which was the respondent's preferred brand and named each botulinum toxin injection brand available in the UK. Another question similarly named all the brands. None of the botulinum toxin injections currently marketed were licensed for the treatment of primary headache or migraine. Question 19a asked 'Are you currently aware of the use of botulinum toxins for any type of primary headache or migraine?'. Question 22 asked clinicians to choose which one of four statements best described their usage intentions of botulinum toxins for headaches/migraine assuming that such a use was officially approved. The third statement read 'I am not interested in trying botulinum toxins for headache/migraine patients, neither injecting them or referring them, unless they become a very common and successful treatment for headache/migraine'. The Panel considered that the nature of the questions and the survey's broad distribution to over 800 clinicians was such that it went beyond merely seeking information and opinion from senior clinicians actively involved in the management of primary headache and migraine conditions as submitted by Allergan. The questions would stimulate interest in the use of botulinum injections for an unlicensed indication. In the Panel's view the survey was a marketing tool which was subject to the Code.

The Panel noted the complainant's primary concern regarding the lack of NICE guidance about the use of botulinum toxins to treat primary headache or migraine but noted that providing the relevant marketing authorization had been granted medicines could be promoted before NICE guidance on their use had been issued. Similarly, the promotion of medicines did not have to be in accordance with any such guidance. In this regard the Panel did not consider that Allergan had failed to maintain high standards as alleged. No breach of the Code was ruled.

The Panel noted that the complainant had also made a broader allegation about the boundaries of honest medicine promotion. The Panel considered that the survey would stimulate interest in the use of botulinum toxins as a class for primary headache or migraine although none of the products

currently marketed were licensed for such use. A clinical study into such use had been presented at the 2009 IHS meeting and Allergan was planning a US licence extension for Botox to include migraine. The survey did not give disproportionate weight to any specific botulinum toxin. The Panel considered that in so much as the survey promoted all botulinum toxins it also promoted Botox. If this were not the case then the effect would be for companies to promote classes of medicines as a means of avoiding the restrictions in the Code. The Panel considered that the survey promoted Botox in a manner which was inconsistent with the particulars listed in its summary of product characteristics (SPC). A breach of the Code was ruled, which was upheld on appeal by Allergan. Botox did have a marketing authorization and so in that regard the Panel ruled no breach of the Code.

The Panel considered that the material at issue promoted botulinum toxins in the guise of a survey. In that regard the promotional activity was disguised and the Panel ruled a breach of the Code, which was upheld on appeal by Allergan. The Panel noted its ruling that the survey was promotional material. It thus followed that it was not a market research activity or the like as referred to the Code. No breach of the Code was ruled.

The Panel considered that given the survey was not a market research activity but promotional and solicited an interest in unlicensed indications the attached cheque for £35 was wholly inappropriate. A breach of the Code was ruled. Upon appeal by Allergan the Appeal Board was concerned that the payment of a fee for completing a study that was ruled in breach of the Code was unacceptable. However the Appeal Board considered that the payment of £35 was not in itself an inducement to prescribe Botox. Thus no breach of the Code was ruled.

The Panel considered that, overall, high standards had not been maintained. A breach of the Code was ruled, which was upheld on appeal by Allergan. The Panel further considered that the content and distribution of the marketing study were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. Upon appeal by Allergan the Appeal Board did not consider the circumstances were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

The Panel was very concerned about all the arrangements for the survey and noted that over 800 clinicians had each been sent £35. In the Panel's view the cheque would encourage them to read and complete the marketing study which promoted a class of products for an unlicensed indication. The Panel reported Allergan to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. Given its rulings above, however, the Appeal Board decided to take no further action.

A consultant neurologist complained about a survey headed 'Neurology Pharmaceutical Survey' sent by a market research agency which consisted of two pages of 22 questions and sub-questions. Nine questions, ie all but one, on page 2 related to the use of botulinum toxin injections. Six of the questions specifically referred to the use of botulinum toxin injections for the treatment of primary headache or migraine.

The accompanying letter from the agency described the survey as a marketing study on the management of primary headache and migraine conditions. It was being carried out on behalf of a pharmaceutical company which had a specific interest in individual clinicians' treatment practice in this therapy area. The letter further stated that as this was a marketing study as opposed to a market research study participants would be identifiable to the company commissioning the research. A cheque for £35 was also included.

Allergan marketed Botox (botulinum toxin). Botox was not licensed for the treatment of primary headache or migraine.

COMPLAINT

The complainant provided a copy of the material at issue, together with part of a poster of the more successful trial presented at the recent International Headache Society (IHS) meeting in Philadelphia (Dodick *et al* 2009). The complainant found it hard to believe this that 'marketing study' was not a means of assembling large numbers of willing users of the medicine before the National Institute for Health and Clinical Excellence (NICE) had established whether the modest (though mathematically significant) improvement over the effect of placebo was cost-effective.
The complainant queried whether Allergan (through its agent) had strayed over the boundaries of honest promotion.

The identity of the commissioning pharmaceutical company was not clear from the documentation. The agency confirmed that it was Allergan Limited.

When writing to Allergan the Authority asked it to respond in relation to Clauses 2, 3.1, 3.2, 9.1, 12.1, 12.2 and 18.1 of the Code.

RESPONSE

Allergan submitted that the Neurology Pharmaceutical Survey was not a promotional activity. These types of surveys were routinely undertaken in the UK and Europe by many pharmaceutical companies and other healthcare organisations. They were designed to gain market intelligence to enable companies to communicate effectively with health professionals with the aim of minimising irrelevant approaches by pharmaceutical personnel. Allergan provided a statement from the agency which gave additional background information on this matter.

The complainant alleged there was some link between data presented at the recent IHS meeting in Philadelphia and the survey. The poster provided by the complainant was not enclosed with the survey. No clinical data was enclosed with the survey and there was no reference or link to clinical results of any kind in either the letter or the survey.

Allergan commissioned the Neurology Pharmaceutical Survey to seek information and opinions from senior health professionals actively involved in the management of primary headache and migraine conditions. Allergan would use the information to develop a deeper understanding of the market and assist with the communication and development of its products and services in this area. It would enable Allergan, in the future, to communicate more effectively with health professionals and ensure these communications were effectively targeted. Whilst some of the information provided might assist in the way products or services were marketed, this did not make the survey promotional.

The survey was conducted in accordance with the British Market Research Society (MRS) regulations, 'Using Research Techniques for Non-Research Purposes'. To comply with these regulations the survey was termed a marketing study rather than a market research study. The distinction between market research and marketing studies was made as a result of data protection considerations.

A market research study aimed to gather market intelligence from a selected group of individuals. Typically an agency contacted individual respondents directly to ask various questions. The answers were not reported back in named form to the sponsor, rather the data was aggregated. Market research was by its nature therefore confidential. The market research community commonly accepted that where a survey was not confidential, ie the sponsor wished to see identified results, then this should not be termed market research. Therefore, the letter to potential participants stated that the survey was 'a marketing study as opposed to a market research study'. The sole reason for this was that participating health professionals would be identifiable to Allergan. It was important from a data protection perspective that the potential participants knew this before they participated in the survey.

The survey and letter were sent to 805 senior neurologists in the UK (14 of whom were professors).

Further contact with recipients depended on their response to the data protection notice at the bottom of the survey. If they opted in and agreed to potential contact to undertake further surveys of this type (ie marketing studies) in the future, then Allergan could conduct further surveys, should it choose to, although none were planned.

Allergan did not believe the survey itself was promotional. The survey was not disguised promotion, it was a legitimate way to gain market intelligence regarding current practice around the treatment and understanding of primary headache and chronic migraine conditions. Therefore, the survey was not in breach of either Clause 12.1 or 12.2.

The questions aimed to obtain detailed market intelligence regarding current practice around the treatment and understanding of primary headache and chronic migraine conditions. There was limited mention of brand names in the survey, only when the question specifically required it (questions 17 and 18 only). Where product was mentioned it was balanced fairly across all brands currently available and did not focus on a specific one vs its competitors. In addition, participants would not know which company commissioned the survey. Allergan denied breaches of Clauses 3.1 and 3.2.

Regarding payment, cheques for £35, addressed to individual doctors, were enclosed with the survey. The reason for enclosing the cheque was explained to the potential participant in the accompanying letter. This approach was widely used for market research or market study surveys to overcome the main problem of some participants not receiving their honorarium, or not receiving it quickly enough. Potential respondents were asked to dispose of the cheque if they were not interested in participating.

The amount paid (£35) was calculated in line with the European Pharmaceutical Market Research Association (EphMRA) Pharmaceutical Market Research Code of Conduct (Clause 3.1) which stated that:

> 'Where an interview is conducted with a 'professional' respondent such as a doctor, or with a member of staff of an organisation such as a hospital, it may be necessary and appropriate to recompense that person or organisation for the amount of their working time taken up by the interview. Such incentives or rewards to respondents should be kept to a minimum level proportionate to the amount of their time involved, and should not be more than the normal hourly fee charged by that person for their professional consultancy or advice.'

Allergan did not consider the payment of £35 was an inducement. Firstly, the survey was not linked to a particular product; there was limited mention of any brand names and where a brand was mentioned, it was balanced fairly across all those currently available and did not focus on a specific one vs its competitors. In addition, participants would not know which company commissioned the survey. £35 was an appropriate recompense for the time required to undertake the survey; it was in line with the EphMRA Code of Conduct. The letter accompanying the survey asked the recipient to dispose of the cheque and questionnaire if they did not wish to participate. Therefore, the survey was

not in breach of Clause 18.1.

Allergan was confident that this activity was not in breach of the Code and, in particular, was not in breach of either Clause 9.1 or Clause 2.

The survey was examined by two senior employees of Allergan, as required by the supplementary information to Clause 14.3 – Examination of Other Material. The survey was considered to comply with the specific requirements of the Code. This item was examined, rather than certified.

In summary, Allergan re-iterated that the scientific data included by the complainant was not enclosed with the survey and was not linked to the survey. The survey was not promotional in nature; it was conducted in accordance with British MRS Regulations. In order to comply with these regulations the survey was termed a marketing study rather than a market research study due to data protection considerations. The agency had run this type of survey for three years with a number of pharmaceutical companies.

In response to a request for further information Allergan stated that there was no NICE guidance on the use of botulinum toxin generally, or Botox specifically, in the management of primary headache or migraine. Further, this topic was not on the current list of NICE clinical guidelines in development.

Allergan provided a printout of the online NHS database for new medicines. The entry for botulinum A toxin (Botox) showed that Allergan was planning a US licence extension to include migraine. Details of any such plans in the UK were confidential.

PANEL RULING

The Panel noted Allergan's submission that the purpose of the Neurology Pharmaceutical Survey was to seek information and opinion from senior health professionals actively involved in the management of primary headache and migraine conditions. The information gained would ensure that Allergan's communications were effectively targeted. Allergan did not argue that the survey was market research outside the scope of the Code but described it as a marketing survey as the participants would be identified to the company. Allergan had examined the survey in relation to the requirements of the Code as non promotional material under the supplementary information to Clause 14.3.

The Panel considered that market intelligence gathering was a legitimate business activity. Such activity had to comply with the Code. Clause 12.2 of the Code required that market research must not constitute disguised promotion and must be conducted with a scientific or educational purpose. The supplementary information to Clause 12.2, Market Research, stated that market research was the collection and analysis of information and must be unbiased and non-promotional. The use to which the statistics or information was put might be promotional. The two phases must be kept distinct. Attention was drawn to guidelines – The Legal and Ethical Framework for Healthcare Market Research – produced by the British Healthcare Business Intelligence Association (BHBIA) in consultation with the ABPI. It was further stated that market research material should be examined to ensure that it did not contravene the Code. The Panel noted that Paragraph 4 of The Legal and Ethical Framework for Healthcare Market Research stated that the principle of the confidentiality was the most crucial distinction between market research and most other forms of marketing activity. The Panel noted that it was consideration of these data protection issues which had led to the survey being described by Allergan as a marketing study. The Code did not make such a distinction. Paragraph 4 of The Legal and Ethical Framework for Healthcare Market Research also stated that, as an activity market research was quite distinct from, *inter alia*, database building.

The Panel examined the survey. The Panel noted that most of the questions on page 2 of the survey referred to the use of botulinum toxin injections. Six of the questions referred to the use of such injections for the treatment of primary headache or migraine. One question asked which was the respondent's preferred brand and named each botulinum toxin injection brand available in the UK. Another question similarly named all the brands. None of the botulinum toxin injections currently marketed were licensed for the treatment of primary headache or migraine. Question 19a asked 'Are you currently aware of the use of botulinum toxins for any type of primary headache or migraine?'. Question 22 asked clinicians to choose which one of four statements best described their usage intentions of botulinum toxins for headaches/migraine assuming that such a use was officially approved. The third statement read 'I am not interested in trying botulinum toxins for headache/migraine patients, neither injecting them or referring them, unless they become a very common and successful treatment for headache/migraine'. The Panel considered that the nature of the questions and the survey's broad distribution to over 800 clinicians was such that it went beyond merely seeking information and opinion from senior clinicians actively involved in the management of primary headache and migraine conditions as submitted by Allergan. The questions were such that they were designed to stimulate interest in the use of botulinum injections for an unlicensed indication. In the Panel's view the survey was a marketing tool which was subject to the Code.

The Panel noted the complainant's primary concern regarding the lack of NICE guidance about the use of botulinum toxins to treat primary headache or migraine but noted that providing the relevant marketing authorization had been granted

medicines could be promoted before NICE guidance on their use had been issued. Similarly, the promotion of medicines did not have to be in accordance with any such guidance. In this regard the Panel did not consider that Allergan had failed to maintain high standards as alleged. No breach of Clause 9.1 was ruled.

The Panel noted that the complainant had also made a broader allegation about the boundaries of honest promotion.

The Panel considered that the survey would stimulate interest in the use of botulinum toxins as a class for primary headache or migraine although none of the products currently marketed were licensed for such use. A clinical study into such use had been presented at the 2009 IHS meeting and Allergan was planning a US licence extension for Botox to include migraine. The survey did not give disproportionate weight to any specific botulinum toxin. The Panel considered that in so much as the survey promoted all botulinum toxins it also promoted Botox. If this were not the case then the effect would be for companies to promote classes of medicines as a means of avoiding the restrictions in the Code. The Panel considered that the survey promoted Botox in a manner which was inconsistent with the particulars listed in its summary of product characteristics (SPC). A breach of Clause 3.2 was ruled. Botox did have a marketing authorization and so in that regard the Panel ruled no breach of Clause 3.1.

The Panel considered that the material at issue promoted botulinum toxins in the guise of a survey. In that regard the promotional activity was disguised and the Panel ruled a breach of Clause 12.1. The Panel noted its ruling that the survey was promotional material. It thus followed that it was not a market research activity or the like as referred to in Clause 12.2. No breach of that clause was ruled.

Clause 18.1 of the Code stated that no gift, benefit in kind or pecuniary advantage should be offered or given to members of the health professions as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clause 18.2. The Panel considered that given the survey was not a market research activity but promotional and solicited an interest in unlicensed indications the attached cheque for £35 was wholly inappropriate. A breach of Clause 18.1 was ruled.

The Panel considered that, overall, high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel further considered that the content and distribution of the marketing study were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was very concerned about all the arrangements for the survey and noted that over 800 clinicians had each been sent £35. In the Panel's view the cheque would encourage them to read and complete the marketing study which promoted a class of products for an unlicensed indication. The Panel decided to report Allergan to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY ALLERGAN

Allergan submitted that the survey was not promotional in either its intent or execution. The crux of this case was the Panel's ruling that the survey was promotional. All the other rulings of breaches derived from this ruling and thus fell with it. Allergan considered that, on the evidence, the survey should be viewed as a legitimate non-promotional business activity.

Allergan submitted that the survey was developed with agency and complied with The Legal and Ethical Framework for Healthcare Market Research produced by the BHBIA in consultation with the ABPI. The aim of the survey was to gain market intelligence on the level of interest in Botox in anticipation of a licence variation currently under review by the Medicines and Healthcare Products Regulatory Agency (MHRA) for a new indication of chronic migraine. Earlier surveys had demonstrated widespread off-label use by British neurologists. The aim of the survey was to collect market information necessary to assist Allergan in its preparations and planning for the launch of Botox for a new indication. It was intended that the data collected would be used as input in modelling and planning for the optimal and affordable size of the sales force required to support the market launch of Botox subject to marketing authorization. Botox would essentially constitute a new unique therapy in this new indication, for which there were currently no or few treatment options. Hence, as the target market was not currently well characterised, the need for collecting first hand market information was even more critical in order to make wise investment and hiring decisions.

Allergan submitted that a drug utilisation study, which it conducted at the request of regulatory bodies to support an EU risk management plan, had established that there was currently extensive off-label use of botulinum toxins. Allergan's intention, therefore, was to design a survey to identify those neurologists who were already interested in the use of botulinum toxins in headache/migraine and who would, therefore, be likely to welcome information on the new indication for Botox, once this had been granted. The purpose of the survey was not to promote within the survey or encourage use in migraine but to enable Allergan to provide the profession with appropriate and targeted information on the new indication, but only once the change to the marketing authorization had been approved by the regulatory authorities.

Allergan noted that Clause 12.2 of the Code expressly provided that, while market research, ie

the collection and analysis of information, must be unbiased and non-promotional, the use to which the information was put might be promotional. It followed, therefore, that Allergan could not be in breach of the Code by its future intention to use the survey results to promote a prescription only medicine in accordance with the SPC only once this had been amended to include the new indication. Moreover, the Panel had stated in its ruling that market intelligence gathering was a legitimate business activity.

Allergan provided a copy of the signed and agreed project proposal with the agency which clearly described the intended use of the data following the launch of the new indication.

Allergan re-iterated that the scientific data included by the complainant was not enclosed with the survey and was not referenced in, or linked in any way to it. The Panel referred to 'a clinical study at the 2009 IHS meeting'. This data was not referenced or cited in the survey.

Allergan noted that 'marketing study' was used for a specific reason in the context of the survey. A more detailed explanation was given below but, in summary, market research had to be confidential. Where the participant was identifiable (with their consent), as in the case of the survey, then it strictly could not be termed market research. The typical terminology used was 'marketing study'. However, this term should not suggest that the survey was promotional. The survey was conducted in accordance with the British MRS regulations, 'Using Research Techniques for Non-Research Purposes'. To comply with these regulations the survey was termed a marketing study rather than a market research study. The distinction between market research and marketing studies reflected important data protection considerations. A market research study sought to gather market intelligence from a selected group of individuals and typically involved the appointment of an agency by a sponsor company. The agency would contact individual respondents directly in asking various questions. The answers were not reported back in named form to the sponsor, rather the data was aggregated or in the form of a report. Market research was by its nature confidential.

Allergan submitted that the methodology used in this survey (ie that it was nominative) meant that it was not, strictly speaking, market research but might be referred to as a 'marketing study' or 'database building'. Allergan referred to Paragraph 4.3 of the BHBIA framework document (February 2008) and paragraph 4c of the updated version (November 2009). This made it clear that database building was a legitimate activity so long as the appropriate data protection rules were observed ie that the participants were fully informed of the use to which their data would be put. This condition was completely fulfilled by the information set out at the bottom of page 2 under the legend in bold 'IMPORTANT DATA PROTECTION NOTICE'. Allergan accepted that that the Code did not expressly refer to the distinction between these two activities but it did refer to the BHBIA framework, which was developed in consultation with the ABPI. It must follow, therefore, that both the ABPI and the PMCPA endorsed the analysis contained in the Framework and this was what guided Allergan and the agency in designing the study.

Allergan submitted that this was why the letter to potential participants stated that the survey was 'a marketing study as opposed to a market research study'. The sole reason for this was that participating health professionals would be identifiable to Allergan. It was important from a data protection perspective that the potential participant knew this before participating in the survey.

Allergan submitted that two senior employees examined the survey, as required by the Code (supplementary information to Clause 14.3 – Examination of Other Material) and considered that it complied with the Code and was non-promotional.

Allergan submitted that the survey was not promotional. The aim of the questions was to obtain detailed market intelligence regarding current practice around the treatment and understanding of primary headache and migraine conditions. There was limited mention of product brands in the survey, and then only when the question specifically required it. Where product was mentioned it was balanced fairly across all brands mentioned and did not focus on a specific product vs its competitors. Allergan noted that participants were not aware of the company commissioning the survey. Clause 1.2 of the Code defined promotion as '... any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'. Nothing in the survey promoted Botox. No claims were made for Botox and no comparisons were made with other products. Botox was not singled out for any special mention. Brand names were only used in two questions where the brand names of all botulinum toxins available in the UK were used. The real focus of the questions was the use of botulinum toxins as a class but the survey was not designed to stimulate interest in the use of botulinum toxins. It was designed to measure interest. The survey was targeted at neurologists, specialists in the management of headache and migraine and the use of botulinum toxins and produced a snapshot of their current practice and future intentions.

Allergan submitted that more specifically, regarding section 3 (page 2) of the survey, question 16 established current use of botulinum toxins across a range of indications, both on and off-label. Questions 17 and 18 related to the use of toxins in any aspect of a neurologist's work, and local product availability. Question 19 established current usage, if any, for headache or migraine – that botulinum toxins were used in this way by some

neurologists was established in a recent drug utilisation study commissioned at the request of the regulatory authorities. Questions 20 and 21 established, where applicable, referral patterns for patients treated with botulinum toxin, and how this might change in the future. Question 22 noted that use for migraine/headache was not currently approved, it then went on to establish future intentions. More specific details regarding the rationale behind the questions in section 3 of the survey were detailed in a supporting letter provided to Allergan by the agency along with examples of similar questions from other studies completed in the UK. In all cases Allergan considered that these were legitimate, non-promotional questions which contained no material which could properly be described as encouraging the prescription of botulinum toxins as a class or Botox in particular. The survey was a legitimate business activity designed to gain data for potential future promotional use.

Allergan submitted that the arrangements for paying the survey participants were in line with the BHBIA Framework and accepted practice in market research. Cheques for £35, made out to individual doctors, were enclosed with the survey; the reason for this was explained to the potential participant in the accompanying letter. This approach was widely used for market research or market study surveys to overcome the main problem of some participants not getting their honorarium or not getting it quickly enough. Along with the explanation for the enclosure of the cheque, potential respondents were asked to dispose of the cheque if they were not interested in participating. Allergan reiterated that the amount paid was calculated in line with the EphMRA – Pharmaceutical Market Research Code of Conduct (Clause 3.1).

Further contact with the recipients depended on their response to the data protection notice at the bottom of the survey. If they opted in and agreed to potential contact to undertake further surveys of this type (ie marketing studies) in the future then Allergan had the option to conduct further surveys, should it choose to, although none were planned at this time.

Allergan submitted that the nature of the survey, with the option for potential future contact, was the reason why the survey was sent to 805 senior neurologists. Unlike market research where a small sample might be sufficient, here the aim was to develop a target list of individuals who were interested in the relevant disease area, had experience of using botulinum toxins or would consider referring patients to another specialist for this treatment if it became available.

The survey was mailed to 805 consultants to avoid any inadvertent bias in the sample as a result of selecting a certain target audience. Further, the greater the response, the higher the statistical robustness of any subsequent analysis for statistical modeling purposes. However, given that a response rate of less than 100% was anticipated (20-40% was usual for this type of survey), it was standard practice to send the survey to the broader consultant universe in order to reach statistical significance when the universe was small. The study focused on regional discrepancies in prescribing behavior as well as individual physician needs and interests. It was essential to have as many respondents as possible (ideally 250 to 300) in order to perform the non-biased targeting and segmentation analysis at this level of granularity.

Allergan hoped that the supporting declaration from the agency provided further reassurance around both the intent and execution of this survey. The format used for these questions was standard practice and commonly used in market research studies where a company investigated perceptions to product concepts before investing in market launch preparation activities.

Allergan submitted the 'Neurology Pharmaceutical Survey' was conducted in accordance with the Code and most importantly that the survey was non-promotional. A number of these kinds of studies were run in the UK and Europe by a number of pharmaceutical companies and other healthcare organisations. The aim was to obtain detailed market intelligence regarding current practice around the treatment and understanding of primary headache and chronic migraine conditions. There was limited mention of product brands in the survey, only when the question specifically required it (Q17 and Q18 only). Where product was mentioned it was balanced fairly across all brands currently available and did not focus on a specific one vs its competitors. In addition, the participants were not aware of the company commissioning the survey.

Allergan fully understood the Panel's concerns that these questions might be considered promotional. However, in the context of a marketing survey, with a target audience of senior neurologists, Allergan submitted that this was not the case for the reasons outlined above. There was never any intent for this to be a promotional activity, the survey was solely designed as a tool to assist potential future targeting of communications. Allergan denied a breach of Clause 3.2.

As stated above, Allergan submitted that the survey itself was not promotional. The nature of the survey was made clear to the recipient of the letter. As explained above, to comply with MRS regulations, the survey must be called a marketing study. The distinction between market research and marketing studies was made as a result of data protection considerations. The survey was not disguised promotion, it was a legitimate way to gain market intelligence about treatment and understanding of primary headache and chronic migraine conditions. Allergan denied a breach of Clause 12.1

Allergan submitted that the survey was not promotional and therefore the payment of £35 was

not an inducement; it was appropriate recompense for the time required to undertake the survey. The amount paid was calculated in line with the EphMRA Pharmaceutical Market Research Code of Conduct (as outlined above). The covering letter asked the recipient to dispose of the cheque and questionnaire if they did not wish to participate. Allergan denied a breach of Clause 18.1.

Allergan was very concerned to be ruled in breach of Clauses 2 and 9.1; the company took its commitment to the Code very seriously. The survey was never designed as a promotional activity, disguised or otherwise. Allergan submitted that as it had fully taken account of the BHBIA framework referred to in Clause 12.2 of the Code and taken this as the appropriate standard, it should not be possible to conclude that high standards had not been maintained. Taking into account MRS regulations this was a legitimate non promotional market intelligence gathering survey to aid future effective targeting of communications with neurologists. The industry could not be brought into disrepute by Allergan's adherence to the very guidelines to which attention was drawn in the supplementary information to Clause 12 of the Code as well as to other sets of guidelines drawn up by bodies with a special responsibility for setting standards in market research.

Allergan submitted that the survey was, in itself, non-promotional in intent and execution. Allergan denied any breach of the Code and particularly any breach of either Clauses 9.1 or 2.

COMMENTS FROM THE COMPLAINANT

The complainant was confident that the argument that Allergan's method of promoting the prescription of botulinum toxin for headache fell outside the Code would be made to the Appeal Board. The complainant remained unconvinced that NICE would ever see that the likely costs of this treatment were supported by sufficiently robust clinical evidence of superiority over placebo in a group of very suggestible patients. Allergan might submit that it had done a 'marketing study', but it was transparently obvious that this was being done to assemble a list of willing users of the medicine, in order that sales were well established before the costs were fully appreciated.

ALLERGAN'S COMMENTS ON THE REPORT FROM THE PANEL

Allergan did not submit any written comments on the report from the Panel but its representatives at the appeal hearing noted that in Allergan's view the survey at issue was a standard, legitimate activity. The company had tried very hard to comply with the guidelines and it did not consider that the survey was promotional.

APPEAL BOARD RULING

The Appeal Board noted Allergan's submission that there was currently extensive off-label use of botulinum toxins. Allergan was hoping to be granted a licence extension for the use of Botox in the treatment of chronic migraine. Allergan submitted that the purpose of the Neurology Pharmaceutical Survey was to asses the level of interest amongst neurologists in using botulinum toxins in headache/migraine. Once Allergan's licence extension had been granted it planned to contact interested responders with information on Botox injections for the treatment of chronic migraine. Allergan would also use the data from the survey to determine the resources it would need to support the launch of the proposed new indication. The Appeal Board considered that market intelligence gathering was a legitimate business activity. Such activity had to comply with the Code.

The Appeal Board noted that most of the questions on page 2 of the survey referred to the use of botulinum toxin injections either as a class or by brand. Six of the questions referred to the use of such injections for the treatment of primary headache or migraine. In that regard the Appeal Board noted that the proposed new indication for Botox was specifically chronic migraine, not primary headache or migraine. The Appeal Board considered that the questions were too specific with regard to the treatment at issue and also that they differed in that regard from some of the more open sample questions provided by the agency. In the Appeal Board's view neurologists reading the survey would get the impression that a botulinum toxin injection would soon become a licensed treatment for headache/migraine. The Appeal Board considered that surveys such as the one at issue might well stimulate interest in a new treatment for a particular condition; this was not necessarily unacceptable. However the Appeal Board did not consider that reasonable steps had been taken with the survey in question to prevent the identification of the medicine at issue. The nature of the questions and the broad distribution of the survey were such that it went beyond seeking opinion and would stimulate interest in the use of botulinum toxin for an unlicensed indication. The Appeal Board considered that in so much as the survey promoted all botulinum toxins it also promoted Botox. If this were not the case then the effect would be for companies to promote classes of medicines as a means of avoiding the restrictions in the Code. The Appeal Board considered that the survey promoted Botox in a manner which was inconsistent with the particulars listed in its SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was not successful.

The Appeal Board considered that the material at issue promoted botulinum toxins in the guise of a survey. In that regard the promotional activity was disguised and the Appeal Board upheld the Panel's ruling of a breach of Clause 12.1. The appeal on this point was not successful.

There were concerns that the payment of a fee for

completing a study that was ruled in breach of Clause 3.2 was unacceptable. However the Appeal Board considered that the payment of £35 to complete the survey was not in itself an inducement to prescribe Botox as prohibited by Clause 18.1. Thus no breach of Clause 18.1 was ruled. The appeal on this point was successful.

The Appeal Board considered that, overall, high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1; the appeal on this point was not successful. The Appeal Board did not consider the circumstances were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled. The appeal on this point was successful.

Given its rulings above the Appeal Board decided to take no further action in relation to the Panel's report, made to it in accordance with Paragraph 8.2 of the Constitution and Procedure.

Complaint received **7 October 2009**

Case completed **25 January 2010**

DOCTOR v GLAXOSMITHKLINE

Sponsorship of a supplement

A doctor complained about a supplement entitled 'ProState of the Nation Report. A call to action: delivering more effective care for BPH [benign prostatic hyperplasia] patients in the UK' sponsored by GlaxoSmithKline which was distributed, *inter alia*, with the Health Service Journal of 22 October. One of the forewords to the supplement was from the chief executive of Prostate UK.

The complainant noted that the declaration on the supplement did not state that Prostate UK received funding from GlaxoSmithKline (in addition to any honoraria paid to the chief executive if she sat on the editorial board). The complainant believed that the funding received by the charity from GlaxoSmithKline constituted a conflict of interest to which readers of the supplement should have been made aware.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that the supplementary information to the Code required that the declaration of sponsorship be sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset. The declaration must accurately reflect the nature of the company's involvement. The Code required that sponsorship of material be declared, not the background relationships between the parties to a project.

The Panel noted GlaxoSmithKline's submission regarding its support of Prostate UK and its declaration of interest in that regard. The supplement at issue was not Prostate UK material that had been supported by GlaxoSmithKline.

The Panel noted that GlaxoSmithKline's corporate logo appeared on the bottom left hand corner of the front page above the statement 'GSK has sponsored the production of this supplement; for details please see the back cover page of the report'. The corporate logo also appeared on the lower left hand corner of the back outside cover alongside the statement 'GSK sponsorship has included payment for a medical writer, honoraria to the editorial board and payment to a public relations agency in respect of project management support'.

The Panel considered that GlaxoSmithKline's role in the production of the supplement had been made clear. Sufficient details appeared prominently on the front page with further explanation on the outside back cover. The Panel noted GlaxoSmithKline's explanation of its sponsorship of certain Prostate UK activities. Prostate UK had not received any monies from GlaxoSmithKline in respect of the report. Honoraria were paid directly to individual board members including those who held positions at Prostate UK. The Panel considered that the sponsorship of the report and membership of the editorial board were transparent. That Prostate UK received sponsorship monies from GlaxoSmithKline in respect of other projects did not preclude its chief executive officer from being a member of the editorial board for the supplement at issue. GlaxoSmithKline's sponsorship of activities by Prostate UK which were unrelated to its sponsorship of the report did not have to be declared in the report at issue. No breach of the Code was ruled.

A doctor complained about a supplement (ref ADT/MAM/09/43437/1) entitled 'ProState of the Nation Report. A call to action: delivering more effective care for BPH [benign prostatic hyperplasia] patients in the UK' sponsored by GlaxoSmithKline UK Ltd which was distributed, *inter alia*, with the Health Service Journal of 22 October 2009. One of the forewords on page 2 of the supplement was from the chief executive of the charity Prostate UK.

COMPLAINT

The complainant alleged that the supplement at issue was in breach of Clause 9.10 of the Code. The supplementary information for Clause 9.10 stated that, 'The declaration [of sponsorship] must accurately reflect the nature of the company's involvement'. The complainant noted that the declaration on the supplement did not state that Prostate UK (whose chief executive officer endorsed the supplement on page 2), received funding from GlaxoSmithKline (in addition to any honoraria paid to her if she sat on the editorial board). The complainant referred to a Prostate UK press release as evidence of this funding.

The complainant believed that the funding received by the charity from GlaxoSmithKline constituted a conflict of interest to which readers of the supplement should have been made aware.

RESPONSE

GlaxoSmithKline stated that it had been transparent in both its sponsorship of the supplement and in its support of various activities organised by Prostate UK and therefore denied the alleged breach of Clause 9.10.

GlaxoSmithKline explained that the supplement

was developed to raise awareness of BPH as an important medical condition which affected the ageing male. GlaxoSmithKline sponsored the report and briefed the medical writer. The report was reviewed and approved by an expert editorial board which had final editorial control. It was intended that the report should be entirely non promotional and solely focus on disease awareness. The report did not include the names of any specific medicines.

GlaxoSmithKline noted that it paid honoraria to members of the editorial board and for the service of a public relations agency to include project management, engaging and liaising closely with a professional medical writer and organising artwork and printing.

The report was published as a sponsored supplement to the Health Service Journal (22/10/2009) and PULSE (21/10/2009). It was also distributed at a BPH awareness event at the House of Commons (19/10/2009), which was hosted by a member of parliament, organised by Prostate UK and sponsored by GlaxoSmithKline. The report would also be distributed to NHS health professionals and budget holders by GlaxoSmithKline representatives.

GlaxoSmithKline noted that the front cover of the report featured the company logo and the statement 'GSK has sponsored the production of this supplement; for details please see the back cover page of the report'. The back cover also featured the GlaxoSmithKline logo and a statement that 'GSK sponsorship has included payment for a medical writer, honoraria to the editorial board and payment to a public relations agency in respect of project management support'. Readers would have a clear understanding of GlaxoSmithKline's involvement in the production of the report.

GlaxoSmithKline explained that Prostate UK was a registered charity which funded medical research and the training of health professionals, provided free public information on a range of prostate diseases and campaigned to raise public awareness without any government funding. GlaxoSmithKline had worked with Prostate UK on the following activities aimed at promoting awareness of BPH over the past year:

- GlaxoSmithKline along with a number of other organisations sponsored a Prostate UK disease awareness campaign ('Pants in the Park'), consisting of six sponsored fun runs across the UK in 2009. The events were held to increase awareness of prostate disease and raise money for the charity. GlaxoSmithKline's sponsorship was £5,000. As a result of these fun runs, Prostate UK raised £50,000. GlaxoSmithKline's sponsorship was clearly disclosed in material promoting the events, an example of which was provided.

- GlaxoSmithKline sponsored and attended an event at the House of Commons (19/10/2009) which was organised by Prostate UK and hosted by a member of parliament. The event was to generate publicity for a submission made to the National Institute for Health and Clinical Excellence (NICE) by Prostate UK for the inclusion of BPH within the Quality and Outcomes Framework. GlaxoSmithKline contributed £5,285 to cover the cost of room hire, refreshments and invitations. GlaxoSmithKline's sponsorship was clearly explained in material promoting the event, an example of which was provided.

- GlaxoSmithKline sponsored the production of a film which Prostate UK developed to support its BPH awareness activities. GlaxoSmithKline contributed £11,500 to cover the costs of producing this film. Editorial control for the film lay entirely with Prostate UK. GlaxoSmithKline's role in sponsoring the film was clearly explained on-screen at both the start and end of the film.

- Prostate UK used a public relations agency which was retained by GlaxoSmithKline to assist in drafting a number of its promotional items, including press releases, about events that had been sponsored by GlaxoSmithKline. Editorial control for these items lay with Prostate UK. However, since they covered events sponsored by GlaxoSmithKline, these items were all reviewed for factual accuracy and compliance with the Code by GlaxoSmithKline. Specifically, GlaxoSmithKline asked for changes to be made in order to clarify and increase transparency in respect of its role in sponsoring these events.

  One such item was the Prostate UK press release cited by the complainant, which was designed to raise awareness of the launch of its BPH disease awareness campaign and was reviewed by GlaxoSmithKline for factual accuracy and Code compliance. GlaxoSmithKline asked for the wording 'with funding from GlaxoSmithKline UK Limited (GSK)' in paragraph 1 and 'which was produced by GSK in conjunction with Prostate UK' in paragraph 6 to be added following its review of a draft sent to it by Prostate UK.

GlaxoSmithKline submitted that it developed the report and paid honoraria to an expert editorial board which had final editorial control. The editorial board comprised:

- Chairman of the editorial board, consultant urologist at the Prostate Centre and medical director of Prostate UK
- Chief executive officer of Prostate UK
- General practitioner with a specialist interest in urology
- Executive director for system reform and service innovation.

Board members were required to attend one face-to-face editorial board meeting, review a number of drafts and write a foreword for inclusion in the report. Honoraria were paid directly to the two

members of the board who also held positions with Prostate UK rather than to the charity itself. Further, Prostate UK had not and would not, receive any monies from GlaxoSmithKline in respect of the report.

In conclusion, GlaxoSmithKline submitted that the complaint related to the complete and accurate declaration of GlaxoSmithKline's involvement in the report. GlaxoSmithKline's involvement was clearly and fully explained within the report. This involvement included payment of honoraria to editorial board members who also held positions within Prostate UK. All members of the editorial board were remunerated in their personal capacity, therefore Prostate UK received no monies from GlaxoSmithKline in respect of this report.

For activities where Prostate UK had received support from GlaxoSmithKline, as described previously, the nature of GlaxoSmithKline's support had been described in a detailed and transparent manner.

GlaxoSmithKline was committed to and took pride in maintaining high ethical standards. The company considered that it had upheld high standards in terms of both its sponsorship of the report and its ongoing relationship with Prostate UK. GlaxoSmithKline denied a breach of Clause 9.10.

PANEL RULING

The Panel noted that the supplementary information to Clause 9.10, Declaration of Sponsorship, required that the declaration of sponsorship be sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset. The declaration must accurately reflect the nature of the company's involvement. Clause 9.10 required that sponsorship of material be declared, not the background relationships between the parties to a project.

The Panel noted GlaxoSmithKline's submission regarding its support of Prostate UK and its declaration of interest in that regard. The supplement at issue was not Prostate UK material that had been supported by GlaxoSmithKline.

The Panel noted that GlaxoSmithKline's corporate logo appeared on the bottom left hand corner of the front page above the statement 'GSK has sponsored the production of this supplement; for details please see the back cover page of the report'. The corporate logo also appeared on the lower left hand corner of the back outside cover alongside the statement 'GSK sponsorship has included payment for a medical writer, honoraria to the editorial board and payment to a public relations agency in respect of project management support'. The report discussed disease impact and treatment options, gave summaries of current UK guidance vs the reality of management for GPs, specialists and patients in the UK, and of the NHS cost burden. The report ended with a call to action which urged the NHS to recognize BPH management and treatment as a key health priority. Treatment options and classes of medicine were discussed. No specific medicines were mentioned. The four members of the editorial board were introduced on the inside front cover including the chief executive officer at Prostate UK. GlaxoSmithKline had submitted that two members of the editorial board held positions at Prostate UK, the identity of the second ie the chairman of the editorial board who was the medical director of Prostate UK, was not clear from the report.

The Panel considered that GlaxoSmithKline's role in the production of the supplement had been made clear. Sufficient details appeared prominently on the front page with further explanation on the outside back cover. The Panel noted GlaxoSmithKline's explanation of its sponsorship of certain Prostate UK activities. Prostate UK had not received any monies from GlaxoSmithKline in respect of the report. Honoraria were paid directly to individual board members including those who held positions at Prostate UK. The Panel considered that the sponsorship of the report and membership of the editorial board were transparent. That Prostate UK received sponsorship monies from GlaxoSmithKline in respect of other projects did not preclude its chief executive officer from being a member of the editorial board for the supplement at issue. GlaxoSmithKline's sponsorship of activities by Prostate UK which were unrelated to its sponsorship of the report did not have to be declared in the report at issue. No breach of Clause 9.10 was ruled.

Complaint received **2 November 2009**

Case completed **18 December 2009**

PRIMARY CARE TRUST PRESCRIBING ADVISOR v FLYNN PHARMA

Distaclor MR email

The prescribing advisor to a teaching primary care trust (PCT) complained about an advertisement, emailed to GPs by Flynn Pharma, which promoted the prescribing of Distaclor (cefaclor) for patients following influenza as they might be susceptible to secondary bacterial respiratory tract infections. The email offered recipients starter packs of Distaclor. Cefaclor was a second-generation, broad-spectrum cephalosporin.

Distaclor MR was indicated in the treatment of a number of listed infections when caused by susceptible strains of the given organism. The summary of product characteristics (SPC) stated that studies to identify the causative organism and its susceptibility to cefaclor should be performed. Therapy might be started pending the outcome of the studies and adjusted when the results became available.

The complainant submitted that the use of broad-spectrum antibiotics was highly likely to increase the risk of resistance to antibiotics, and also led to the emergence of infections such as *Clostridium difficile*. In that regard the Health Protection Agency (HPA) had stressed that narrow-spectrum agents should be used for empirical treatment where appropriate and that the use of clindamycin and second and third-generation cephalosporins should be avoided, especially in the elderly.

The complainant stated that the local prescribing team endorsed the HPA guidance and that of local experts and considered that the advertisement, which offered free samples, went against that guidance and was surely inappropriate.

The detailed response from Flynn Pharma is given below.

The Panel noted that Flynn had offered starter packs not samples. The Code defined starter packs as a small pack designed to provide sufficient medicine for a primary care prescriber to initiate treatment when there might be an unavoidable delay in having a prescription dispensed. Antibiotics were appropriate to be given in starter packs.

The Panel considered that the mailing was confusing in that the content of the starter pack was not made clear; the starter pack offer was repeated immediately after reference to the calendar packs of 14 tablets. Flynn had submitted that the starter packs contained two tablets. Starter packs were not samples and thus not subject to the requirements of the Code which regulated the supply of samples. No breach of the Code was ruled in that regard.

The Panel noted that the advertisement stated that influenza might leave patients susceptible to secondary bacterial respiratory tract infections. Such patients might appreciate a free starter pack if seen out of hours or when the local pharmacy was closed. This was followed by two questions 'Do you have the time or the resources to find out which organism is responsible for your patients' secondary respiratory infections?' and 'Or do you need to prescribe a broad spectrum antibiotic which covers the most common bacterial causes?' followed by 'If so, consider Distaclor'.

The Panel noted that the complainant's PCT prescribing team discouraged the use of second- and third-generation cephalosporins in primary care as advised by the HPA and local experts. The Panel noted, however, that provided a medicine was promoted in such a way that was not inconsistent with its SPC, it was not necessarily unacceptable under the Code if that promotion was not in line with local or national guidelines.

In this instance the Panel considered that although the HPA advised against the use of, *inter alia*, second-generation cephalosporins, the advertisement at issue was not inappropriate as alleged. No breach of the Code was ruled.

Given its rulings above the Panel did not consider that high standards had not been maintained.

A prescribing advisor to a teaching primary care trust (PCT) complained about an advertisement for Distaclor (cefaclor) emailed by Flynn Pharma Ltd. Cefaclor was a second-generation, broad-spectrum cephalosporin.

The email in question had the subject header 'Flu season, free antibiotic starter packs'. The heading to the advertisement was 'Give your patients a head start with Distaclor MR starter packs'.

Distaclor MR was indicated in the treatment of a number of listed infections when caused by susceptible strains of the given organism. The summary of product characteristics (SPC) stated that studies to identify the causative organism and its susceptibility to cefaclor should be performed. Therapy might be started pending the outcome of the studies and adjusted when the results became available.

COMPLAINT

The complainant noted that the advertisement, emailed to GPs, promoted the prescribing of cefaclor for patients following influenza, as they might be susceptible to secondary bacterial respiratory tract infections.

The advertisement stated: 'Do you have the time or resources to find out what organism is responsible for your patients' secondary respiratory infections?'. It then offered free antibiotic starter packs, 14 days of cefaclor.

The complainant submitted that unnecessary use of broad-spectrum antibiotics was highly likely to increase the risk of resistance to antibiotics, and also led to the emergence of infections such as Clostridium difficile. In that regard the Health Protection Agency (HPA) stated in its guidance 'Clostridium difficile infection: How to deal with the problem' that restrictive antibiotic guidelines should be developed by trusts with the following recommendations stressed:

- Use narrow-spectrum agents for empirical treatment where appropriate.
- Avoid use of clindamycin and second- and third-generation cephalosporins, especially in the elderly.

The complainant's PCT prescribing team was dedicated and committed to advising prescribers on the appropriate use of antibiotics to ensure that they were used only when absolutely necessary. It strongly discouraged the prescribing of second- and third-generation cephalosporins in primary care, as advised by the HPA and local microbiologists, in an attempt to prevent the emergence of C.difficile. The advertisement at issue, which promoted the use of a broad-spectrum antibiotic and offered free samples, went against the HPA's advice and was surely inappropriate.

When writing to Flynn Pharma, the Authority asked it to respond in relation to Clauses 7.10, 9.1, 17.1 and 17.12 of the Code.

RESPONSE

Flynn stated that it knew that the incidence of C.*difficile* infections caused concern and naturally it supported activities which would lead to a reduction in the number of cases of this debilitating, and sometimes fatal, infection.

Flynn did not accept that the advertisement was in breach of the Code. In relation to the alleged breach of Clause 17 (provision of medicines and samples), the advertisement clearly offered 'starter packs' as distinct from 'samples' in this case two doses of treatment sufficient for a primary care prescriber to initiate treatment where there might be some undesirable or unavoidable delay'. The mailing specifically stated that the value of the starter packs was in the 'out of hours' situation and/or when 'the local pharmacy is closed'. This was in reality a question of good practice the benefits of which were generally recognised. Flynn appreciated however that the mailing did not specify the content of the starter pack as being two tablets and this would be amended in any subsequent communication.

Clause 7.10 required that promotion encouraged the rational use of a medicine. With regard to the specific complaint, the test was whether Flynn had inappropriately sought to encourage the use of a broad-spectrum antibiotic. The context of the mailing made clear in bold print statements that Distaclor might be considered where the prescriber did not have 'the time or resources to find out which organism is responsible' (for the secondary respiratory infection). Secondly it then specifically asked the prescriber to consider, 'do you need to prescribe a broad spectrum antibiotic…? 'and 'If so, consider Distaclor'. Flynn respectfully submitted that this was neither inappropriate or irrational. Broad-spectrum antibiotics were an important prescribing option in circumstances described and in particular, in primary care. The HPA and prescribing advisors were rightly concerned about indiscriminate and injudicious use. Flynn agreed with this position and need and hence the careful positioning and conditions for prescribing Distaclor were set out in the mailing.

Finally in regard to any alleged breach of Clause 9.1 (high standards), Flynn did not see that there was any case to answer.

Flynn submitted that it was an incontrovertible fact that influenza could lead to secondary bacterial respiratory tract infections through local damage to the respiratory tract epithelium and/or the development of a compromised immune function.

Faced with a patient recovering from influenza who presented with symptoms of a secondary bacterial upper respiratory tract infection (URTI) or lower respiratory tract infection (LRTI) a GP had three basic options.

- Send a sputum sample to an appropriate laboratory for culture and sensitivity. Then recall the patient when the results were available (48 hours or more later) and, if appropriate, prescribe antibiotic(s) to cover the sensitivity of the organism(s) detected. This delayed treatment and might significantly increase the severity of the condition to be treated and increase the complication rate leading to significant morbidity and even mortality.

- Empirical treatment with an antibiotic with an appropriate spectrum of activity. The most common, community acquired, bacterial causes of respiratory tract infections were: *Streptococcus pneumoniae, Haemophilus influenzae* beta lactamase (BL-), *Haemophilus influenzae* (BL+), *Moraxella catarrhalis* (BL-), *Moraxella catarrhalis* (BL+) and *Staphylococcus*

aureus. Cefaclor was active against all these bacteria, whereas a 'narrow-spectrum' antibiotic would not be. A chart containing similar information and references was included in the advertisement.

- A combination of the two options above ie obtain a sputum sample for culture and sensitivity and treat empirically. Recall the patient if the initial antibiotic was inappropriate.

In clinical practice the second and third options outlined above were almost universally followed in general practice and the approach outlined in the advertisement was consistent with good medical practice. The advertisement offered prescribers free starter packs (of 2 tablets, not 14 days of treatment) to commence treatment out-of-hours ie if they saw patients when the local pharmacy was closed. This was, again, consistent with good medical practice and offered the benefit of immediate commencement of treatment.

As a background the normal bacterial flora in the gut served as the major barrier against colonization by *C. difficile*. In general, the composition of the normal microflora was remarkably stable. The flora could be altered, however, by such factors as antimicrobial therapy, diet, pathological conditions, and gastrointestinal tract surgery. Of these, antimicrobial therapy was the most frequent cause of disturbance to the normal oropharyngeal and intestinal flora.

In a review of the pathophysiology of antibiotic-associated diarrhoea and colitis, Hooker *et al* (1988) noted that the alterations in normal gastrointestinal flora were often the result of incomplete oral absorption of antibiotics. Bergan (1986) noted in a review article that 'The better the bioavailability, i.e., the amount of oral dose reaching the systemic circulation, the less the amounts spilled into the colonic lumen. High amounts of drug within the colon would represent both an economic waste and have high potential of influencing the fecal flora'. Therefore, an antibiotic that was incompletely absorbed was likely to have a significant effect on the bowel flora.

Virtually every antibiotic could alter the gastrointestinal flora, leading to the proliferation of potentially pathogenic bacteria, such as *C. difficile.* Cefaclor, whilst having a broad spectrum of activity, was nearly 95% absorbed; in a healthy volunteer study where subjects received 750mg of Cefaclor daily for 7 days no medicine was detected in the faeces (Nord *et al* 1986).

Nord *et al* (1987) studied the impact of orally administered cefaclor, penicillin, erythromycin, bacampicillin, clindamycin, doxycycline, metronidazole, norfloxacin and ciprofloxacin on intestinal microflora. Pronounced alteration of the intestinal flora occurred in patients who received clindamycin and erythromycin, whereas only moderate changes were observed in patients who received doxycycline and ciprofloxacin. Penicillin, bacampicillin, cefaclor and metronidazole produced only minor changes in the intestinal flora.
Nord *et al* (1986), assessed the impact of cefaclor, 250mg every 8 hours, on the normal human oropharyngeal and intestinal microflora in 10 healthy adults. No marked effects on the aerobic oropharyngeal microflora were apparent. Also, no new oropharyngeal colonization occurred. Cefaclor caused only minor changes in the intestinal microflora. Anaerobic cocci decreased, while other anaerobic bacteria remained unaffected. Within 1 week post-therapy the anaerobic microflora returned to normal in all subjects. None of the volunteers experienced gastrointestinal side effects. The authors stated that with other antibiotics 'the alteration of the aerobic microflora has led to undesirable consequences such as superinfections and C. difficile intestinal diseases'. The findings in the present investigation indicated that cefaclor had minor ecological impacts on the normal human oropharyngeal and intestinal microflora.

The HPA guidance '*Clostridium difficile* infection: How to deal with the problem' stated: 'Use narrow-spectrum agents for empirical treatment where appropriate', 'Avoid use of clindamycin and second- and third-generation cephalosporins, especially in the elderly'. This document, however, presented no data on the risk of second- or third-generation cephalosporins in causing *C. difficile* infections. No references in this document reviewed this topic; the basis of the position taken in this document was another HPA document.

The HPA document '*Clostridium difficile* infection: How to deal with the problem – a board to ward approach, draft for comment' stated in Section 4 that third-generation cephalosporins had been strongly associated with *C. difficile* infection and that 'effective restriction of third generation cephalosporins was associated with a reduction in *C.difficile* infections'. The review presented no data on second-generation cephalosporins.

This review also did not refer to Levy *et al* (2000) which involved 358,389 ambulatory patients and analysed the prevalence of *C.difficile* diarrhoea (CDD) and the risk for this associated with different oral antibiotics commonly used in the ambulatory care setting. The study showed that different antibiotics were associated with varying degrees of risk for CDD eg a first-generation cephalosporin (cefalexin), and a third-generation cephalosporin (cefixime) were associated with a higher relative risk for CDD than other antibiotics assessed. There were no cases of *C.difficile* associated with cefaclor in 15,966 risk periods.

Of 8,346 patients evaluated for safety in cefaclor clinical trials, gastrointestinal reactions, especially diarrhoea, nausea or vomiting (either alone or in combination), occurred in 209 (2.5%). Cefaclor treatment was discontinued in 55 of these patients (0.6%). Two reports of gastroenteritis occurred, and there were no reports of pseudomembranous colitis (Hislop 1988).

The impact of a wide number of antimicrobial agents on the human intestinal microflora was reviewed by Nord and Edlund (1990). At recommended doses and for recommended duration of treatment only cefaclor demonstrated a lack of effect on intestinal flora. This review also supported the change in 'classification' of cefaclor from high to low risk when given at recommended doses and a recommended duration of therapy.

Given the spectrum of activity and side effect profile of cefaclor the advertisement in question was consistent with good medical practice and the scientific literature available and that specific to cefaclor itself, and did not encourage the development of unwarranted cases of *C. difficile* infection.

Flynn noted the Department of Health's (DoH's) attitude was implicit in its recent public tender for oral antibiotic stocks for reserve in anticipation of a UK H1N1 pandemic (offer reference CM/EMI/08/5034). In that tender the DoH sought offers for the supply of up to 10,690,000 courses of oral co-amoxiclav (or doxycycline), a broad-spectrum antibiotic intended for use primarily in the community. The evidence to support the use of co-amoxiclav in preference to cefaclor was unclear. In contrast, Flynn found, as was supported by the evidence described above, that cefaclor was indiscriminately presumed 'guilty' by association – in other words a class effect which was not supported by the evidence. Still further, Flynn noted, as set out in the advertisement, the evidence in support of cefaclor in preference to co-amoxiclav where gastrointestinal side effects were a concern.

PANEL RULING

The Panel noted that Flynn had offered starter packs not samples. The Code defined starter packs as a small pack designed to provide sufficient medicine for a primary care prescriber to initiate treatment when there might be an unavoidable delay in having a prescription dispensed. Antibiotics were mentioned as a type of medicine which could appropriately be given in starter packs.

The Panel considered that the mailing was confusing in that the content of the starter pack was not made clear; the starter pack offer was repeated immediately after reference to the calendar packs of 14 tablets. Flynn had submitted that the starter packs contained two tablets. Starter packs were not samples. Clauses 17.1 and 17.12 referred only to samples. Thus the Panel ruled no breach of Clauses 17.1 and 17.12.

The Panel noted that the advertisement stated that influenza might leave patients susceptible to secondary bacterial respiratory tract infections. Such patients might appreciate a free starter pack if seen out of hours or when the local pharmacy was closed. This was followed by two questions 'Do you have the time or the resources to find out which organism is responsible for your patients' secondary respiratory infections?' and 'Or do you need to prescribe a broad spectrum antibiotic which covers the most common bacterial causes?' followed by 'If so, consider Distaclor'.

The Panel noted that the complainant's PCT prescribing team discouraged the use of second- and third-generation cephalosporins in primary care as advised by the HPA and local experts. The Panel noted, however, that provided a medicine was promoted in such a way that was not inconsistent with its SPC, it was not necessarily unacceptable under the Code if that promotion was not in line with local or national guidelines.

In this instance the Panel considered that although the HPA advised against the use of, *inter alia*, second-generation cephalosporins, the advertisement at issue was not inappropriate as alleged. No breach of Clause 7.10 was ruled.

Given its rulings above the Panel did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

Complaint received **20 November 2009**

Case completed **9 February 2010**

CASE AUTH/2278/11/09

CHILD AND ADOLESCENT PSYCHIATRIST v LUNDBECK

Promotion of Circadin

A child and adolescent psychiatrist complained about the promotion of Circadin (prolonged release melatonin) by Lundbeck. Circadin was indicated for the short-term treatment of primary insomnia in patients aged 55 or over. It was not recommended for use in children or adolescents below the age of 18 due to insufficient data on safety and efficacy.

The complainant was concerned to find a number of items of stationery advertising Circadin in his clinic. A Lundbeck representative had given them to a paediatrician colleague who had asked for information about Circadin. Although child psychiatrists and paediatricians sometimes prescribed melatonin off licence to children, Circadin was only licensed for the over 55 age group. The complainant's service and all the services in his building worked exclusively with children and so distributing promotional material to a paediatrician seemed to be promoting an unlicensed indication.

The detailed response from Lundbeck is given below.

The Panel noted that the complainant had not seen the Lundbeck representative. The health professional who had seen the representative did not consider that Circadin had been promoted outside the terms of its marketing authorization. The health professional stated that she and other colleagues would not infrequently prescribe melatonin for sleep disorders in children and that she had found the meeting useful as she and her colleagues had learned that the tablet had to be swallowed whole as crushing would affect its efficacy.

The Panel was concerned that the representative had responded to a request from a paediatrician at a children's centre for information about Circadin which was not recommended for use in children due to insufficient data on safety and efficacy. According to the paediatrician the representative had made it clear both before and at the meeting that he could only talk about the licensed use of Circadin and not its use in children. In the Panel's view it would have been more appropriate for the company's medical information department to respond to the paediatrician's request. However there was no complaint about the meeting; the allegation concerned the provision of promotional aids. The Panel was concerned that following a conversation about a product with a health professionals who would not be expected to use it within its marketing authorization, the representative had left promotional aids for that product. The Panel considered that the representative had not maintained a high standard of ethical conduct and a breach of the Code was ruled.

The Panel did not consider that providing promotional aids which consisted solely of the brand name and company name constituted promotion that was inconsistent with the SPC. No breach of the Code was ruled.

The Panel considered that the briefing material supplied by Lundbeck might have benefited from being clearer regarding the licensed indication. A key message appeared to imply that Lundbeck had more choice in the positioning rather than the only positioning being in patients older than 55 years. However, a list of questions which representatives should refer to medical information included 'Is there any evidence for use in children?', 'What if a clinician wants to use Circadin in young age groups?'. Overall the Panel did not consider that the briefing material advocated a course of action that was likely to lead to a breach of the Code. No breach of the Code was ruled.

The Panel noted that promotional material should only be given to those categories of persons whose need for or interest in the particular information could reasonably be assumed. The promotional aids did not contain any information about Circadin other than its brand name and the company name. The Panel did not consider that in these circumstances Lundbeck had breached the Code.

A child and adolescent psychiatrist at a children's centre complained about the promotion of Circadin (prolonged release melatonin) by Lundbeck Ltd.

Circadin was indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients aged 55 or over. It was not recommended for use in children or adolescents below the age of 18 due to insufficient data on safety and efficacy.

COMPLAINT

The complainant was concerned to find a number of items of stationery advertising Circadin in his clinic. A Lundbeck representative had given them to a paediatrician colleague who had asked for information about Circadin.

Although child psychiatrists and paediatricians sometimes prescribed melatonin off licence to children, Circadin was only licensed for the over 55 age group. The complainant's service and all the

services in his building worked exclusively with children and so distributing promotional material to a paediatrician seemed to be promoting an unlicensed indication.

The complainant was advised by the Authority that this might be a breach of the Code. This case might throw up wider issues if Circadin was being promoted in this way in other child and adolescent/paediatric services.

When writing to Lundbeck, the Authority asked it to respond in relation to Clauses 3.2, 11.1, 15.2 and 15.9 of the Code.

RESPONSE

Lundbeck confirmed that a specialist paediatrician, at a community area mental health service, specifically requested a meeting with one of its representatives to discuss some of the scientific matters associated with Circadin. The representative did not discuss the use of Circadin in children/adolescents and at all times during the meeting acted within his remit and discussed the product within the terms of the summary of product characteristics (SPC). The representative gave the paediatrician a copy of the Circadin SPC. Lundbeck enclosed written testimony from the paediatrician to confirm this account.

The representative left some post-it notes and pens in response to a specific request from a member of the reception staff. No material containing promotional messages was left at the centre.

The representative in question had passed the ABPI examination.

Lundbeck provided a number of relevant items for sales force training or for use with customers which it submitted clearly stated:

- Circadin was positioned for use within the licensed indication
- Circadin was indicated for use in patients aged 55 years or older
- Circadin was not recommended for use in children and adolescents
- Circadin was not licensed for children or attention deficit hyperactivity disorder (ADHD)
- Questions regarding evidence in children/use in young persons should be referred to the medical information department

Lundbeck stated categorically that it was not its policy to promote Circadin for use in this patient population either through the use of its sales force or any other method.

PANEL RULING

The Panel noted that the complainant had not seen the Lundbeck representative. The health professional who had seen the representative did not consider that Circadin had been promoted outside the terms of its marketing authorization. The health professional stated that she and other colleagues would not infrequently prescribe melatonin for sleep disorders in children and that she had found the meeting useful as she and her colleagues had learned that the tablet had to be swallowed whole as crushing would affect its efficacy.

Lundbeck submitted that no material containing promotional messages was left at the centre. The representative had left branded post-it notes which also included the company name and pens which bore the brand name.

The Panel was concerned that the representative had responded to a request from a paediatrician at a children's centre for information about Circadin which was not recommended for use in children due to insufficient data on safety and efficacy. According to the paediatrician the representative had made it clear before and at the meeting that he could only talk about the licensed use of Circadin and not its use in children. Representatives must always ensure that their conduct complied with the Code regardless of their customers' wishes. In the Panel's view it would have been more appropriate for the company's medical information department to respond to the paediatrician's request rather than a representative. However there was no complaint about the meeting; the allegation concerned the provision of promotional aids. The Panel was concerned that following a conversation about a product with a health professional who would not be expected to use it within its marketing authorization, the representative had left promotional aids for that product. The Panel considered that in providing the promotional aids in these circumstances the representative had not maintained a high standard of ethical conduct and a breach of Clause 15.2 was ruled.

The Panel did not consider that providing promotional aids which consisted solely of the brand name and company name constituted promotion that was inconsistent with the SPC. No breach of Clause 3.2 was ruled.

The Panel considered that the briefing material supplied by Lundbeck might have benefited from being clearer regarding the licensed indication. It might be argued from the key message 'Circadin will be positioned in new patients > 55 years with primary insomnia alongside sleep hygiene' was ambiguous and implied that Lundbeck had more choice in the positioning rather than the only positioning being in patients older than 55 years. However, a list of questions which representatives should refer to medical information included 'Is there any evidence for use in children?', 'What if a clinician wants to use Circadin in young age groups?'. Overall the Panel did not consider that the briefing material advocated a course of action that was likely to lead to a breach of the Code. No

breach of Clause 15.9 was ruled.

The Panel noted that Clause 11.1 required that promotional material should only be given to those categories of persons whose need for or interest in the particular information could reasonably be assumed. The promotional aids did not contain any information about Circadin other than its brand name and the company name. The Panel did not consider that in these circumstances Lundbeck had breached Clause 11.1 and thus no breach was ruled.

Complaint received **20 November 2009**

Case completed **28 January 2010**

CASE AUTH/2279/11/09

VOLUNTARY ADMISSION BY PROCTOR & GAMBLE

Breach of undertaking

Procter & Gamble voluntarily admitted a breach of the Code in that an exhibition guide, which should have been withdrawn pursuant to Case AUTH/2267/9/09, was put into the delegate bags for an international congress held in the UK.

The Authority's Constitution and Procedure provided that a voluntary admission should be treated as a complaint if it related to a potentially serious breach of the Code or if the company failed to take action to address the matter. The reuse of material previously ruled in breach was a serious matter and the admission was accordingly treated as a complaint.

Procter & Gamble explained that in Case AUTH/2267/9/09, the strapline 'Confidence in Colitis' was ruled in breach of the Code. As a result, Procter & Gamble immediately recalled and destroyed all relevant materials. After executing a robust and thorough recall process, Procter & Gamble was confident that as per the undertaking, signed on 28 October, these materials were last used on 10 November. However on 18 November, it was discovered that owing to an individual human error the exhibition guide, which contained an Asacol advertisement with the strapline 'Confidence in Colitis', had been overlooked. The exhibition guide had been approved prior to the Panel's ruling but was printed after the Panel's ruling and placed in delegate bags ready for the congress which opened on 21 November.

As soon as it knew of the error Procter & Gamble tried to stop the exhibition guide being distributed. The conference organiser was immediately informed of the situation. Agency workers were allowed into the exhibition centre overnight to remove the material from the delegate bags. No access to the delegate bags was allowed whilst the corrective action was being undertaken and the conference organiser oversaw the removal of material in order to ensure that there was no mixing of 'old' and 'amended' delegate bags. Two company employees were sent to the conference venue the next morning (20 November) to ensure that all of the exhibition guides in question were removed and destroyed. However a sample audit of approximately 5,000 out of the 14,000 delegate showed that a very small minority of delegate bags still contained the exhibition guides at issue.

Procter & Gamble acknowledged that the undertaking was an important document and that this incident was a significant error on its behalf, hence the actions that were immediately implemented as soon as it knew about the situation. As a matter of high priority its standard operating procedure for the recall of promotional materials would be revisited and revised to ensure that all employees followed procedures correctly so incidences such as this one could never happen again.

The detailed response from Procter & Gamble is given below.

The Panel noted that Procter & Gamble had agreed to the printing of the exhibition guide on 15 October and printing commenced on 27 October. Procter & Gamble had been advised of the Panel's ruling in Case AUTH/2267/9/09 on 20 October and the company signed the undertaking on 28 October. The last use of the material at issue was to be 10 November.

The Panel was concerned that the exhibition guide was not included on a job bag tracker spreadsheet. This appeared to be the root cause of the problem. No details were given about how the error came to light on 18 November. The Panel considered that once the error had been identified, Procter & Gamble had made every effort to withdraw the material. Nonetheless when the conference delegates started to arrive on 20 November a small number of delegate bags still contained the exhibition guide in question.

The Panel considered that Procter & Gamble had breached its undertaking and a breach of the Code was ruled as acknowledged by the company. By failing to list the material on the job bag tracker spreadsheet the Panel considered that high standards had not been maintained and a breach of the Code was ruled as acknowledged by Procter & Gamble.

Notwithstanding the considerable action taken by Procter & Gamble to withdraw the material, together with the timing of the printing of the exhibition guide and the provision of the undertaking, the Panel considered that the failure to list the material on the job bag tracker spreadsheet and the resultant distribution of a small number of the exhibition guides reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

Procter & Gamble Pharmaceuticals UK, Limited voluntarily admitted a breach of the Code in that an exhibition guide (ref AS8112) which should have been withdrawn pursuant to Case AUTH/2267/9/09 was put into the delegate bags for Gastro 2009, a large international congress held in the UK.

The action to be taken in relation to a voluntary

admission by a company was set out in Paragraph 5.4 of the Authority's Constitution and Procedure which stated that the Director should treat the matter as a complaint if it related to a potentially serious breach of the Code or if the company failed to take action to address the matter. The reuse of material previously ruled in breach was a serious matter and the admission was accordingly treated as a complaint.

COMPLAINT

Procter & Gamble explained that following notification of the Panel's ruling in Case AUTH/2267/9/09, dated 20 October 2009, it was found in breach of Clause 3.2 in relation to the strapline 'Confidence in Colitis'. Other breaches were also found. As a result, Procter & Gamble immediately implemented its standard operating procedure (SOP) for the recall and destruction of all promotional materials that were subject to these rulings.

After executing a robust and thorough recall process, Procter & Gamble was confident that all affected materials had been successfully accounted for and thus no longer in promotional use. As per the undertaking, signed on 28 October, these materials were last used on 10 November.

However at close of business Wednesday, 18 November, it was discovered that owing to an individual human error one item had been overlooked ie the exhibition guide at issue that had been sponsored by Procter & Gamble. The exhibition guide contained an Asacol advertisement with the strapline 'Confidence in Colitis'. The exhibition guide had been approved by Procter & Gamble prior to the Panel's ruling.

Unfortunately, the exhibition guide was inadvertently printed after the Panel's ruling and placed in the delegate bags to be distributed at the congress which opened on 21 November.

As soon as this error had been identified, Procter & Gamble took the matter extremely seriously and did the following to prevent any of the exhibition guides being distributed.

- The conference organiser was contacted immediately to tell them about the situation and to understand the logistics involved (eg location of delegate bags, etc).
- An agency provided 27 people by 12.30 on 19 November (increasing to 70 people by 17.00) to work overnight and remove the material from the delegate bags.
- The agency workers were given access to an isolated area of the exhibition centre to ensure no public access to the delegate bags whilst the corrective action was being undertaken.
- The conference organiser oversaw the removal of material in order to ensure that there was no mixing of 'old' and 'amended' delegate bags.
- Two Procter & Gamble employees were sent to the conference venue the next morning (20 November) to ensure that all of the exhibition guides in question were removed and destroyed by the agency staff. They also sampled approximately 5,000 out of the 14,000 delegate bags to assess how thorough the operation was.

However despite all of Procter & Gamble's efforts to remove the exhibition guides, on Monday, 23 November it was apparent that, according to its sample audit, a very small minority of delegate bags still contained them.

Procter & Gamble acknowledged that the undertaking was an important document and that this incident was a significant error on its behalf, hence the actions that were immediately implemented as soon as it knew about the situation.

Procter & Gamble noted that the company was acquired by Warner Chilcott UK Ltd on 30 October 2009. As a matter of high priority for the new company, all SOP training processes, including the one for the recall of promotional materials, would be revisited and revised to ensure that all employees followed procedures correctly so incidences such as this one could never happen again. Procter & Gamble would also look to see if the SOP could be made even clearer in terms of instructions to employees.

When writing to Procter & Gamble the Authority asked it to comment in relation to Clauses 2, 9.1 and 25 of the Code.

RESPONSE

Procter & Gamble stated that following notification of the Panel's ruling of 20 October in Case AUTH/2267/9/09, it was found in breach of the Code on three counts: Clause 3.2 relating to the strapline 'Confidence in Colitis' and two other breaches were ruled. Procter & Gamble accepted the breaches and immediately implemented its SOP for the recall and destruction of all promotional materials that were subject to these rulings. This process included an email being sent to the sales force on the day the undertaking was signed (28 October). The email was sent with high importance, a return receipt, and was preceded by a text message sent earlier that day.

After executing what it believed to be a robust and thorough recall process, Procter & Gamble was confident that all affected materials had been successfully accounted for and subsequently no longer in promotional use. As per the undertaking, these materials were last used on 10 November. However at approximately 13:30 on 18 November, it was discovered that the exhibition guide for Gastro 2009 (AS8112; Date of Preparation Oct 2009) had been overlooked. Gastro 2009 was a large international conference held in the UK from 21-25 November. The four page exhibition guide was sponsored by Procter & Gamble. The first page listed all the exhibitors, the inside double spread

showed a map of where all the exhibitors could be found within the conference hall. The back page had an Asacol advertisement which included the strapline 'Confidence in Colitis' previously ruled in breach.

The exhibition guide had been approved and certified on 14 October, ie before the Panel had concluded its rulings in Case AUTH/2267/9/09. On 14 October Procter & Gamble gave its media agency permission to print the guides. On 15 October the media agency sent the approved map to the Gastro 2009 conference organisers for printing. Again this was before both the case rulings and the undertaking was signed by Procter & Gamble on 28 October. Printing of the maps began on 27 October ie before the undertaking was signed.

Unfortunately, the exhibition guide was not identified in the recall process; this was because the material was not included in the Asacol job bag tracker, an internal spreadsheet designed to document all promotional materials relating to Asacol. The recall SOP made it clear and upfront that all items subject to an Authority ruling should be identified. However this was totally dependent on individuals accurately populating the job bag tracker on an on-going basis. Procter & Gamble had already identified this matter as an urgent training gap and as a direct consequence all personnel accountable in the recall SOP, as well as all other relevant SOPs, were retrained on 9 December, with this matter as a poignant example.

As a result of this oversight, 14,000 exhibition guides were in print when the undertaking was signed.

As soon as it knew about the error, Procter & Gamble took the matter seriously and put the following steps into place to prevent any of the exhibition guides being distributed as set out above. Procter & Gamble repeated them below, with further detail, to provide clarity as to the steps taken to rectify the error:

- The conference organisers were advised of the situation by telephone and email and asked about the logistics involved (eg location of delegate bags, etc). Procter & Gamble liaised with the organiser to make the necessary arrangements for the removal of the exhibition guide. An agency provided 27 people by 12:30 on 19 November (increasing to 70 people by 17:00) to work overnight and remove the material from the delegate bags. The agency workers were given access to a designated area of the exhibition centre to ensure no public access to the delegate bags whilst the corrective action was being undertaken.
- The conference organiser oversaw the removal of material in order to ensure that there was no mixing of 'old' and 'amended' delegate bags.
- Two Procter & Gamble employees went to the venue the next morning (20 November), to check that all the exhibition guides had been removed from the delegate bags. They sampled 5,000 out of the 14,000 bags to assess how thorough the operation had been.

However, despite all of Procter & Gamble's efforts to remove the exhibition guide, on Friday 20 November when conference delegates began to arrive, it was apparent that, according to Procter & Gamble's sample audit, a small minority, estimated at approximately < 2%, of delegate bags still contained the exhibition guide.

Procter & Gamble assured the Panel that it had taken this matter extremely seriously and as a top priority for the company the SOP for the recall of promotional material was being appraised. The aim being to ensure the entire process was as robust and thorough as it needed to be. Procter & Gamble had therefore conducted refresher training on all relevant SOPs, on 9 December, for all personnel accountable in these SOPs.

Procter & Gamble was fully committed to comply with its undertaking in relation to Case AUTH/2267/9/09 and realised the importance of this document. This was why Procter & Gamble told the Authority immediately it became apparent that, unfortunately despite all its efforts to stop the exhibition guide being distributed at Gastro 2009, there remained a small chance that not all of the guides had been removed from the 14,000 delegate bags.

Procter & Gamble acknowledged that the requirements for Clause 25 had not been fulfilled and that failing to prevent any of the exhibition guides from being distributed after the undertaking had been signed indicated that high standards had not been met. However Procter & Gamble hoped the Panel would consider that the overall effort to rectify the error, and the urgency behind this effort, was testimony to the company's professional and responsible approach to the matter. This coupled with the fact that on 21 November, when Gastro 2009 opened, only an extremely small number of delegate bags might have contained the incorrect exhibition guide. Procter & Gamble therefore believed its actions, as described above, had not resulted in an incident that had brought the entire pharmaceutical industry into disrepute.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings and that they provided full and accurate details of the last use of material in breach.

The Panel noted that Procter & Gamble had agreed to the printing of the exhibition guide on 15 October and printing commenced on 27 October. Procter & Gamble had been advised of the Panel's ruling in

Case AUTH/2267/9/09 on 20 October and the company signed the undertaking on 28 October. The last use of the material at issue was to be 10 November.

The Panel was concerned that the exhibition guide was not included on the job bag tracker spreadsheet. This appeared to be the root cause of the problem. No details were given about how the error came to light on 18 November. The Panel considered that once the error had been identified, Procter & Gamble had made every effort to withdraw the material. Nonetheless when the conference delegates started to arrive on 20 November a small number of delegate bags still contained the exhibition guide in question. The Panel considered that Procter & Gamble had breached its undertaking and a breach of Clause 25 was ruled as acknowledged by the company. By failing to list the material on the job bag tracker spreadsheet the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled as acknowledged by Procter & Gamble.

With regard to Clause 2, the Panel considered that the relevant factor was whether the circumstances surrounding the breach of undertaking warranted such a ruling. A company must be satisfied that its internal control of promotional material was such that, when called upon to provide an undertaking it could be confident that the information so provided was accurate. It was thus essential that any document designed to list all promotional material was accurately populated and always up-to-date. The Panel considered that Procter & Gamble's actions on discovering the error had been exemplary. If the exhibition guide had been identified when the undertaking was provided, Procter & Gamble would have had to withdraw the guide as a consequence of signing that undertaking.

Notwithstanding the considerable action taken by Procter & Gamble to withdraw the material, together with the timing of the printing of the exhibition guide and the provision of the undertaking, the Panel considered that the failure to list the material on the job bag tracker spreadsheet and the resultant distribution of a small number of the exhibition guides reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **23 November 2009**

Case completed **25 January 2010**

ANONYMOUS DOCTOR v LUNDBECK

Conduct of representative

An anonymous and uncontactable complainant writing as a hospital doctor alleged that the conduct of one of Lundbeck's representatives had been unprofessional and unethical in that she had been accompanied on her visit to him by a representative from another named company. The representatives had spoken about their respective competitor products.

The detailed response from Lundbeck is given below.

The Panel noted that the Authority had not taken this matter up with the other company as the name of its representative was not known.

The complainant had made a very specific complaint about the conduct of a Lundbeck representative but had provided few details. As the complainant was anonymous and non contactable the Panel could not obtain further information. The Panel noted that Lundbeck submitted that its representative had never made a joint visit with a representative from the named company. The Panel noted that the Code was silent on the matter of representatives from competitor companies making joint visits although in its view it would be highly unusual for them so to do. The Panel considered that it had not been provided with any information to show that the Lundbeck representative had breached the Code. No breaches of the Code were ruled.

An anonymous and uncontactable complainant writing as 'a doctor at a [city] hospital', wrote to Lundbeck Ltd, copying his letter to the ABPI which passed his letter to the Authority, which treated the letter as a complaint. The complainant alleged that the behaviour described was unprofessional and unacceptable.

COMPLAINT

The complainant stated that he had been visited by one of Lundbeck's hospital representatives. Under normal circumstances this was appropriate; however he was concerned that a representative from another named company had accompanied the Lundbeck representative. The two representatives had spoken about their respective competitor products and asked the complainant to use whichever one of the two.

The complainant stated that this approach was completely unprofessional and unethical. Never as a doctor had he come across this situation, and been put in an awkward position.

He did not raise his concerns at the time, as he was in utter shock as to what had happened. Colleagues had assured him that this was not allowed by the Code.

The complainant stated that a copy of his letter to the ABPI would name the representative who accompanied the Lundbeck representative.

As a reputable company, the complainant hoped that Lundbeck would take this matter seriously and reprimand/re-train its representative so that this circumstance should not arise in the future.

Doctors' time was precious in treating/saving patients' lives, and situations like this did not bear well in how effectively time was spent. The complainant hoped this was an isolated representative in Lundbeck and not a general tactic.

* * * * *

Contrary to what the complainant stated above, his letter to the ABPI did not name the representative said to have accompanied the Lundbeck representative.

* * * * *

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

RESPONSE

Lundbeck stated that it had met with the named representative and with a number of other Lundbeck employees in the area. Lundbeck had spoken to the named company.

Lundbeck's representative stated categorically that she had never made a joint visit to a customer with a representative from the named company and that in all her years of service she had never made a joint call on a customer with a representative from another company. Lundbeck submitted that of 15 customer visits made by the representative in the relevant area in the past three months four had been accompanied calls; one with her manager and three with other Lundbeck representatives. Lundbeck interviewed those involved in the joint calls and none had ever worked for the named company. The representative in question did not know the named company's local representative.

Without further information it was not possible for Lundbeck to comment further.

PANEL RULING

The Panel noted that the Authority had not taken this matter up with the named company as the identity of its representative was not known.

The complainant had made a very specific complaint about the conduct of a Lundbeck representative but had provided few details. As the complainant was anonymous and non contactable the Panel could not obtain further information. The Panel noted that Lundbeck submitted that its representative had never made a joint visit with a representative from the named company. The Panel noted that the Code was silent on the matter of representatives from competitor companies making joint visits although in its view it would be highly unusual for them so to do. The Panel considered that it had not been provided with any information to show that the Lundbeck representative had breached the Code. No breach of Clauses 15.2 and 15.9 was ruled.

Complaint received **27 November 2009**

Case completed **11 January 2010**

CASE AUTH/2283/12/09

ANONYMOUS v LUNDBECK

Reference to location of prescribing information

An anonymous complainant alleged that on a two page advertisement for Cipralex (escitalopram), placed by Lundbeck in The Pharmaceutical Journal, the statement 'For references and prescribing information, see overleaf' was too small.

The detailed response from Lundbeck is given below.

The Panel noted that the reference to where the prescribing information was to be found was in type such that a lower case 'x' would be smaller than 2mm in height. The Panel ruled a breach of the Code as acknowledged by Lundbeck.

An anonymous complaint was received about the statement regarding the location of the prescribing information in an advertisement for Cipralex (escitalopram) (ref 1009/ESC/501/188) placed by Lundbeck Ltd in The Pharmaceutical Journal, 28 November 2009. The advertisement consisted of two pages, a right hand page followed by a left hand page. The statement 'For references and prescribing information, see overleaf' was approximately two thirds of the way down the right hand page at the end of the right hand column of text and above a table of data.

COMPLAINT

The complainant stated that according to the Code, if the prescribing information was overleaf, there must be a statement on its location such that a lower case 'x' was no less than 2mm in height. The statement in the Cipralex advertisement was too small.

When writing to Lundbeck, the Authority asked it to respond in relation to Clause 4.7 of the Code.

RESPONSE

Lundbeck stated that copy which was sent to the journal had a lower case font size of 1.7mm for the reference regarding the location of the prescribing information. Lundbeck accepted that this did not comply with Clause 4.7 of the Code and it had taken immediate corrective action with respect to this particular advertisement. Lundbeck had also checked other material both in use and in development to ensure that this error had not been repeated.

In addition, Lundbeck had brought this case to the attention of all those involved in the development and approval of promotional material both inside the company and at the advertising agencies it currently used. This was a fundamental error with respect to Code compliance and should not have occurred. All relevant personnel had been reminded of this and of the importance of complying with the Code both to the letter and in spirit.

Lundbeck emphasised that it remained fully committed to the Code at all levels in the organisation. Adherence to the Code featured prominently throughout the activities of the company and personnel received regular training and updates on the Code and its developments.

PANEL RULING

The Panel noted that the reference to where the prescribing information was to be found was in type such that a lower case 'x' would be smaller than 2mm in height. The Panel ruled a breach of Clause 4.7 as acknowledged by Lundbeck. Further, the Panel noted that the reference was not on the outer edge of the advertisement as required by the Code.

Complaint received	**2 December 2009**
Case completed	**26 January 2010**

CONSULTANT NEUROLOGIST v BEACON

Episenta mailing

A consultant neurologist complained that a mailing from Beacon promoting Episenta (prolonged release sodium valproate) included claims that Episenta was bioequivalent to Epilim (sodium valproate; marketed by Sanofi-Aventis) and was interchangeable with it including the modified release formulations (Epilim Chrono). The modified release formulations were not interchangeable for epilepsy and the majority of authorities, including the Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Clinical Excellence (NICE) and various epilepsy guidelines, suggested patients with controlled epilepsy should be prescribed a branded formulation preparation (either named generic or branded) and should not change preparations. A forthcoming article in Drugs and Therapeutics Bulletin was likely to support this view.

The complainant considered that the mailing contradicted the advice that the majority of neurologists currently gave to patients and to GPs about maintaining a named brand supply for patients with epilepsy.

The complainant provided a copy of an article on the relevance of generic prescribing to antiepileptic medicines.

The detailed response from Beacon is given below.

The Panel noted that the Episenta summary of product characteristics (SPC) advised that when changing from sodium valproate enteric coated tablets to Episenta to keep the same daily dose. There was no other advice in the SPC with regard to changing from one anti-epileptic medicine to Episenta.

The Panel noted Beacon's submission that the MHRA had evaluated all the data and concluded that Episenta was bioequivalent to Epilim Chrono.

The Panel noted from the article provided by the complainant that there were concerns about generic prescribing of anti-epileptic medicines.

The Panel noted that two studies by Wangemann compared the bioequivalence of Orfiril 300mg [Episenta] with that of Ergenyl Chrono 300 [Epilim Chrono] in healthy volunteers. Both the single dose study and the five day study concluded [Episenta] met the commonly accepted range of bioequivalence of 80-125% compared with the reference formulation [Epilim Chrono].

The Epilim Chrono SPC stated that it was interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis *in patients where adequate control had been achieved* (emphasis added). The Epilim SPC included similar advice.

It appeared to the Panel that 'interchangeable' in the Epilim SPC meant changing from one product to another for a reason and not the random switching of patients from one brand to another and back again.

Based on the data before it the Panel considered that it was not unreasonable to refer to Episenta and Epilim Chrono being interchangeable as alleged. No breach of the Code was ruled.

A consultant neurologist complained about two letters from Beacon Pharmaceuticals Ltd promoting Episenta (prolonged release valproate).

The mailing at issue had been sent to neurologists and paediatric neurologists. It consisted of a letter (ref 20091021) and a four page leaflet (ref 20091021). The letter included a question 'Would it be useful if [a sodium valproate product] was bioequivalent to, and thus interchangeable with, Epilim or Epilim Chrono?' Followed by a statement that Episenta 'can help achieve these outcomes'. The leaflet included the claims 'Episenta is bioequivalent to Epilim Chrono' and 'Episenta is interchangeable with other conventional or prolonged release formulations of valproate on an equivalent daily dosage basis'.

Sanofi-Aventis marketed Epilim and Epilim Chrono (controlled release sodium valproate).

COMPLAINT

The complainant noted that the letters stated that Episenta was bioequivalent to Epilim and was interchangeable with it including the modified release formulations. The modified release formulations were not interchangeable for epilepsy and the majority of authorities, including the Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Clinical Excellence (NICE) and various epilepsy guidelines, suggested patients with controlled epilepsy should be prescribed a branded formulation preparation (either named generic or branded) and should not change preparations. A forthcoming article in Drugs and Therapeutics Bulletin was likely to support this view.

The complainant considered that the letters contradicted the advice that the majority of neurologists currently gave to patients and to GPs

about maintaining a named brand supply for patients with epilepsy.

The complainant provided a copy of an article on the relevance of generic prescribing to antiepileptic medicines.

When writing to Beacon, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

Beacon noted that the complainant referred to two letters it had sent and provided a copy of one of them. Beacon had sent several mailings in 2009 to all neurologists or paediatric neurologists involved in the management of epilepsy. Despite the wide distribution of these mailings Beacon had received no other enquiries or complaints related to this issue. The statement at issue was:

> **'Episenta is bioequivalent to Epilim Chrono**
> Episenta is interchangeable with other conventional or prolonged release formulations of valproate on an equivalent daily dosage basis.'

Beacon could justify this statement in a number of ways but one of the most relevant was Section 4.2 of the Epilim Chrono summary of product characteristics (SPC), which stated:

'In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.'

Thus the Epilim Chrono SPC supported the view that presentations might be interchangeable. Beacon had discussed various claims which it wanted to make with Sanofi-Aventis in May 2009 and Sanofi-Aventis did not object to the statement above.

Bioequivalence was a key point. Pharmaceuticals in the UK were rigorously assessed by the Medicines and Healthcare products Regulatory Agency (MHRA). In order to gain a marketing authorization for Episenta, Beacon had to establish that it was 'essentially similar' to a reference brand product. One key aspect of essential similarity was bioequivalence.

Two studies were undertaken by Wangemann (1998); one compared the pharmacokinetics of single dose Episenta and Epilim Chrono and the other evaluated steady state kinetics after 5 days' dosing. The author concluded that the presentations did not differ with respect to the rate or extent of absorption.

The MHRA had evaluated all of the available pharmacokinetic data for Episenta capsules and sachets and concluded that it was bioequivalent with Epilim Chrono. The Episenta marketing authorization was granted on the grounds that it was 'essentially similar' to and thus interchangeable with Epilim Chrono.

The complainant mentioned the NICE guidelines. The relevant guideline was Clinical Guideline 20, October 2004, and there were few references made to the point of debate.

Section 4.8.8 of the full guide stated:

> 'Changing the formulation or brand of AED [anti-epileptic drug] is not recommended because different preparations may vary in bioavailability or have different pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side effects.'

This statement carried the lowest D grade recommendation and so was based directly on level 4 evidence or extrapolated from levels 1, 2, or 3.

Beacon submitted that the issue of generic prescribing was not evaluated by NICE as summarised in the following section:

> '11.1.6 Generic prescribing
> This was not a key clinical question, and therefore no evidence review was undertaken. This is an important issue in the prescribing of AEDs, and the prescriber is advised to consult the BNF [British National Formulary] for specific advice for different AEDs. For example, for carbamazepine, the BNF states that 'different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation'; for phenytoin, that 'on the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients'.'

Comments in the BNF on the variable bioavailability of AEDs were restricted to just two products, carbamazepine and phenytoin. The BNF entries were as follows:

> Carbamazepine
> 'Different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation'.
>
> Phenytoin Non Proprietary
> 'On the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients'.

Beacon had not found substantive evidence to support variable bioavailability that was relevant to

products in the UK, even for carbamazepine or phenytoin. The article provided by the complainant supported the view that most evidence was either anecdotal or from uncontrolled studies. Notwithstanding this Beacon supported the view that branded products should be prescribed for patients with epilepsy, particularly where this might affect concordance. Beacon believed this was an important issue for these patients as non-adherence could have serious consequences. Thus, Beacon believed it agreed with the complainant and the main sentiment within the article provided by the complainant.

Beacon emphasised that it did not advocate random switching of patients from one brand of sodium valproate to another, and nor was this stated in its materials. However, a physician might consider changing a patient from another brand of sodium valproate to Episenta where poor adherence might be contributing to poor symptom control. This was the clear message within Beacon's mailing. The simple once daily, night time dose of Episenta coupled with its easy to swallow presentation might be useful attributes in engendering concordance.

Stefan (2006) switched patients from either Epilim or Epilim Chrono to Episenta and concluded:

'It is notable that the number of seizures in more than 90% of patients who were already treated with sustained release valproate (BD) was reduced even further by the switch to the evening dosage regimen. This is presumably due to better compliance.'

The claim regarding bioequivalence was entirely in line with the marketing authorization and therefore complied with the Code.

PANEL RULING

The Panel noted that the Episenta SPC advised that when changing from sodium valproate enteric coated tablets to Episenta to keep the same daily dose. There was no other advice in the SPC with regard to changing from one anti-epileptic medicine to Episenta.

The Panel noted Beacon's submission that the MHRA had evaluated all the data and concluded that Episenta was bioequivalent to Epilim Chrono.

The Panel noted from the article provided by the complainant that there were concerns about generic prescribing of anti-epileptic medicines.

The Panel noted that both Wangemann studies compared the bioequivalence of Orfiril 300mg [Episenta] with that of Ergenyl Chrono 300 [Epilim Chrono] in healthy volunteers. Both the single dose study and the five day study concluded [Episenta] met the commonly accepted range of bioequivalence of 80-125% compared with the reference formulation [Epilim Chrono].

The Epilim Chrono SPC stated that it was interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis **in patients where adequate control had been achieved** (emphasis added). The Epilim SPC included similar advice.

It appeared to the Panel that 'interchangeable' in the Epilim SPC meant changing from one product to another for a reason and not the random switching of patients from one brand to another and back again.

Based on the data before it the Panel considered that it was not unreasonable to refer to Episenta and Epilim Chrono being interchangeable as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this case the Panel noted that the claim in the material that Episenta was interchangeable with other conventional or prolonged release formulation was referenced to the Epilim SPC. The Panel was concerned that the claim implied that the Epilim SPC specifically referred to Episenta which was not so. Further, the Epilim SPC statement referred only to interchangeability in patients who were adequately controlled; the claim in the Episenta promotional material did not refer to adequately controlled patients. The Panel requested that Beacon be advised of its concerns.

Complaint received **8 December 2009**

Case completed **8 February 2010**

CODE OF PRACTICE REVIEW – FEBRUARY 2010

Cases in which a breach of the Code was ruled are indexed in **bold type**.

2198/1/09	**Primary Care Trust v Solvay**	**Patient identification programme**	**Breaches Clauses 2, 18.1 and 18.4** **Audit required by Appeal Board** **Public reprimand by Appeal Board** **Re-audit required by Appeal Board**	**Report from Panel to Appeal Board**	**Page 3**
2258/8/09	**Anonymous v Sanofi-Aventis**	**Conduct of representatives**	**Breach Clause 15.2**	**Appeal by respondent**	**Page 11**
2259/9/09	**Johnson & Johnson/Director v Pfizer**	**Promotion of Champix**	**Breach Clause 2** **Six Breaches** **Clause 7.2** **Two Breaches** **Clause 7.8** **Breaches Clauses 7.3, 7.4, 9.1, and 25**	**No appeal**	**Page 16**
2265/9/09	**Consultant Respiratory Physician**	**Promotion of Symbicort**	**Breach Clause 7.2** **Two Breaches** **Clause 9.1** **Breach Clause 9.3**	**No appeal**	**Page 32**
2267/9/09	**Shire v Procter & Gamble**	**Promotion of Asacol**	**Two Breaches** **Clause 3.2** **Breach Clause 7.2**	**No appeal**	**Page 37**
2270/10/09	**Allergan v Merz Pharma**	**Promotion of Xeomin**	**Breaches Clauses 7.2 and 7.3**	**Appeal by respondent**	**Page 44**
2274/10/09	**Consultant Neurologist v Allergan**	**Marketing survey**	**Breaches Clauses 3.2, 9.1 and 12.1**	**Appeal by respondent** **Report from Panel to Appeal Board**	**Page 49**
2275/11/09	Doctor v GlaxoSmithKline	Journal supplement	No breach	No appeal	Page 58
2277/11/09	Primary Care Trust Prescribing Advisor v Flynn Pharma	Distaclor MR email	No breach	No appeal	Page 61
2278/11/09	**Child and Adolescent Psychiatrist v Lundbeck**	**Promotion of Circadin**	**Breach Clause 15.2**	**No appeal**	**Page 65**
2279/11/09	**Voluntary Admission by Procter & Gamble**	**Breach of undertaking**	**Breaches Clauses 2, 9.1 and 25**	**No appeal**	**Page 68**
2281/11/09	Anonymous Doctor v Lundbeck	Conduct of representative	No breach	No appeal	Page 72
2283/12/09	**Anonymous v Lundbeck**	**Reference to location of prescribing information**	**Breach Clause 4.7**	**No appeal**	**Page 74**
2285/12/09	Consultant Neurologist v Beacon	Episenta mailing	No breach	No appeal	Page 75

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 sponsorship of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

It also covers:

- the provision of information to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. 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.

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 about the promotion of medicines, or the provision of information to the public, should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.