NUMBER 69 AUGUST 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.

PROPOSALS TO AMEND THE ABPI CODE OF PRACTICE FOR THE PHARMACEUTICAL INDUSTRY 2008

Proposals to amend the ABPI Code of Practice for the Pharmaceutical Industry 2008 were agreed by the ABPI Board of Management and posted on the PMCPA website this summer. The consultation has been released in two parts.

Phase one (Appendices 1 & 2) was released on 28 June and closed on 13 August. Appendix 1 included the regular updating of the Code which results mainly from the consideration of cases and requests for guidance. It also included changes relating to increased transparency, for example the proposed changes to Clause 23 regarding payments to patient organisations and the proposed changes to Clause 13 to require publication of the outcome of non-interventional studies. Appendix 2 set out the proposed changes with regard to the use of promotional aids arising from discussions by the ABPI Trust Imperative. It also proposed changes in relation to the ABPI Guidance Notes on Joint Working between Pharmaceutical Companies and the NHS and Others for the Benefit of Patients.

Phase two (Appendix 3) of the consultation was released on 4 August. Responses to this phase should be with the PMCPA if possible by 1 September but by no later than 14 September.

Appendix 3 sets out further proposals to amend the Code in relation to transparency. The proposed changes to Clause 20 will require declaration of the total amount paid to consultants as fees for certain services, together with the number of consultants and the average payment made to them. It does not require the naming of individuals. Similar requirements regarding declarations of sponsorship to attend meetings are proposed under Clause 19. In addition there is a proposal under Clause 18 to require declaration of payments to organisations.

It is anticipated that final proposals will come before the ABPI Half-Yearly General Meeting on 2 November with a view to approval by member companies. If approved, the new Code of Practice would come into effect on 1 January 2011 but with a transitional period before becoming fully operative on 1 May 2011. A longer transitional period is proposed in relation to declaration of payments.

The proposals have been sent to the Medicines and Healthcare products Regulatory Agency (MHRA), the British Medical Association (BMA), the Royal Pharmaceutical Society of Great Britain (RPSGB) and the Royal College of Nursing (RCN) as required by the PMCPA Constitution and Procedure.

Comments on phase two (Appendix 3) should be sent to consultations@pmcpa.org.uk or the Director at Prescription Medicines Code of Practice Authority, 12 Whitehall, London, SW1A 2DY.

CAN THE PANEL'S RULING BE CHANGED?

It is sometimes the case that, having been informed of the Code of Practice Panel's ruling in a case, one or other of the parties will request further information from the Panel as to the reasoning behind its ruling. Occasionally amendments to the Panel ruling might be suggested.

Once the Panel has completed its consideration of a case and informed the parties of the outcome, it has no further role to play in that case. The Panel ruling provides a complete account of the factors in the case that the Panel considered were important in making its ruling.

If either party considers that the Panel has made the wrong ruling for whatever reason then their only recourse is to appeal.

APPOINTMENT OF PMCPA ASSISTANT SECRETARY

The PMCPA will shortly be advertising for an Assistant Secretary. This is a new role which was established to implement changes to the Constitution and Procedure agreed in April 2010. Details will be placed on the PMCPA website.

CODE OF PRACTICE TRAINING

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

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

The next Code of Practice seminar date on which places remain available is:
Monday, 18 October 2010
Monday, 13 December 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.

CASE AUTH/2235/5/09

CEPHALON/DIRECTOR v PROSTRAKAN

Promotion of Abstral

Cephalon complained that a revised promotional campaign for Abstral (sublingual fentanyl citrate tablet) issued by ProStrakan did not accommodate the ruling of a breach of the Code with regard to a 10 minute pain relief claim (Case AUTH/2207/2/09). Not only did the campaign persist with the theme of Abstral being faster in onset than was consistent with its summary of product characteristics (SPC), it actually inferred that Abstral was even faster in onset than the 10 minutes recently ruled in breach and thus appeared to show disregard for the recent ruling.

Cephalon alleged that the advertisement heading, 'To hell and back in minutes' clearly implied that Abstral worked in a few minutes. This was further reinforced in the body of the advertisement by the claim 'Acts in minutes' referenced to the SPC. 'Acts in minutes' also appeared, unreferenced in the strapline.

As made clear in Case AUTH/2207/2/09 the SPC stated that '… Abstral has been shown to induce significantly superior pain relief from 15 minutes after administration onwards, …'. Conversely the above claims implied that it gave pain relief in a few minutes - certainly nowhere near as long as 15 minutes. Cephalon alleged that the claims were grossly misleading and inconsistent with the SPC.

Cephalon further alleged that the issue was sufficiently similar to that recently ruled in breach, such that it was not compliant with the undertaking.

As the complaint included an alleged breach of the undertaking given in Case AUTH/2207/2/09 that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The detailed response from ProStrakan is given below.

The Panel noted that Section 5.1 of the Abstral SPC (Pharmacodynamic properties) stated that '… Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards…'. Section 4.2 of the SPC (Posology and method of administration) stated that 'if adequate analgesia is not obtained within 15-30 minutes of administration of a single sublingual tablet, a second 100 microgram sublingual tablet may be administered'.

In Case AUTH/2207/2/09 the Panel noted that the claim at issue 'Rapid relief of breakthrough cancer pain from 10 minutes' was based upon data from a study but nonetheless considered that it was inconsistent with the particulars listed in the SPC and a breach of the Code was ruled.

The claims now at issue in Case AUTH/2235/5/09 were 'To hell and back in minutes' and that Abstral 'Acts in minutes'. In the Panel's view most readers would not consider 'in minutes' to be as long as the 15 minutes referred to in the SPC; some readers might even consider 'in minutes' to mean less than 10. The advertisement featured three faces of a woman showing how her expression changed as she experienced pain relief. The Panel noted that the claim in full read 'Dissolves in seconds. Acts in minutes'. In the Panel's view the depiction of only three faces and the accompanying claim 'Dissolves in seconds' added to the impression that Abstral acted very quickly. The Abstral SPC was quite specific with regard to timings whereas the advertisement left it to the reader's judgement to decide what 'in minutes' meant. This was unacceptable. Time to onset of action was particularly relevant for a medicine to treat breakthrough cancer pain; it was unhelpful not to give more details. The Panel considered ProStrakan's submission that the claim was consistent with the SPC because it used the same units of time disingenuous. The Panel considered that by not giving more information as to the time that Abstral took to act, the claims 'Acts in minutes' and 'To hell and back in minutes' were misleading and a breach of the Code was ruled. The Panel also considered that each unqualified claim was inconsistent with the particulars listed in the SPC in that most readers would assume that Abstral took less than 15 minutes to act. A breach of the Code was ruled.

The Panel noted that the claim in Case AUTH/2207/2/09, that Abstral gave relief of pain 'from 10 minutes', gave a quicker time to action for the product than stated in the SPC. It was alleged that the claim implied a statistical significance which was inconsistent with the SPC. The Panel had noted the efficacy data but considered nonetheless that the claim was inconsistent with the SPC. The Panel considered that although there were some differences between the two cases the unqualified claims now at issue, 'To hell and back in minutes' and that Abstral 'Acts in minutes', also implied a quicker time to action than stated in the SPC. The Panel further considered that the claims appeared to show a complete disregard for the previous ruling and were sufficiently similar such that they were covered by the undertaking given in that case. A breach of the Code was ruled. High standards had not been maintained; a breach of the Code was ruled.

The Panel considered that the failure to comply with the undertaking reduced confidence in, and brought discredit upon, the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

The Panel was extremely concerned that new material had been developed which might imply to some readers an even quicker time to action than the 10 minute claim previously ruled in breach of the Code. The Panel considered that the failure to comply with the undertaking together with the exacerbation of effect, warranted reporting the company to the Code of Practice Appeal Board for it to consider the matter in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that the advertisement at issue had been used since January 2009 when Abstral was launched in the UK. The advertisement's date of preparation, March 2009, indicated when it had been re-approved following ProStrakan's review of material pursuant to the undertaking given in Case AUTH/2207/2/09. The Appeal Board was concerned that senior managers within the company had considered that the advertisement now at issue was acceptable given the outcome of the previous case.

The Appeal Board noted that ProStrakan had instigated a major review of its compliance policies and procedures (due to be completed by December 2009) and the company's submission that it had strengthened its approval system with the addition of experienced consultants which would be ongoing.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of ProStrakan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in six months' time when ProStrakan's compliance review would be complete. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the audit report the Appeal Board noted that although ProStrakan had improved its processes, procedures and skills there were, nonetheless, still some areas which needed further attention. The Appeal Board decided that ProStrakan should be reaudited. On receipt of the reaudit report the Appeal Board would consider whether further sanctions were necessary.

Upon receipt of the reaudit report the Appeal Board considered that progress had been made since the previous audit in January 2010. The company had plans to ensure maintenance or further improvement of standards. The Appeal Board decided that no further action was required.

Following the adverse rulings in Case Auth/2207/2/09, Cephalon complained about an Abstral (sublingual fentanyl citrate tablet) advertising campaign, issued by ProStrakan.

As the complaint included an alleged breach of the undertaking given in Case AUTH/2207/2/09 that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. ProStrakan was accordingly asked to comment in relation to Clauses 2 and 9.1 of the Code in addition to the clauses cited by Cephalon.

COMPLAINT

Cephalon complained about a revised campaign, purporting to accommodate the recent ruling relating to a 10 minute pain relief claim for Abstral (Case AUTH/2207/2/09). However, not only did it persist with the theme of Abstral being faster in onset than was consistent with the Abstral summary of product characteristics (SPC), it inferred that it was even faster in onset than the 10 minutes recently ruled in breach. As such, it appeared to show disregard for the recent ruling.

Cephalon alleged that the Abstral advertisement placed in the BMJ of 18 April 2009 (ref MO17/0134; Date of preparation: March 2009) clearly implied that Abstral worked in a few minutes by the heading which prominently stated 'To hell and back in minutes', further reinforced in the body of the advertisement by the claim 'Acts in minutes' referenced to the SPC. The wording 'Acts in minutes' also appeared, unreferenced in the strapline.

As made clear in Case AUTH/2207/2/09 the SPC (Section 5.1 Pharmacodynamic properties) stated that '… Abstral has been shown to induce significantly superior pain relief from 15 minutes after administration onwards, …'. This was in sharp contrast to the above claims which implied that it gave pain relief in a few minutes. To clinicians, 'in minutes' would without doubt imply a rapid speed of onset of pain relief, namely a few minutes - certainly nowhere near as long as 15 minutes. Cephalon alleged that the claims were grossly misleading and inconsistent with the Abstral SPC, in breach of Clauses 7.2 and 3.2.

Cephalon requested that the advertisement, and any other items making similar claims in the current campaign, be reviewed with regard to its concerns outlined above, in particular bearing in mind the recent ruling that a 10 minute claim for pain relief was ruled in breach of Clause 3.2.

Cephalon alleged that the breaches outlined above persisted in giving the seriously misleading impression that the speed of onset of pain relief was considerably faster than the 10 minutes recently ruled in breach for being inconsistent with the 15 minutes stated in the Abstral SPC. Cephalon further alleged that the issue was sufficiently similar

to that recently ruled in breach, such that it was not compliant with the undertaking in breach of Clause 25.

RESPONSE

ProStrakan denied that the claims at issue were in breach of Clauses 7.2 and 3.2 of the Code. The claims 'To hell and back in minutes' and 'Acts in minutes' were accurate, fair and unambiguous descriptions of the onset of effect of Abstral and were not inconsistent with the SPC.

ProStrakan submitted that Section 5.1 of the Abstral SPC stated that the product had shown 'significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards'. The claim 'Acts in minutes' was therefore consistent with the SPC which used minutes as the unit of time to describe the onset of effect. It would have been misleading to represent the onset of effect in terms of a smaller unit of time (seconds) but the SPC described efficacy as being seen in terms of minutes. Breakthrough cancer pain was a 'transitory' or 'transient' exacerbation of pain. Abstral was specifically licensed to treat this type of rapid onset, short-lived pain. Therefore the claim 'To hell and back in minutes' was an accurate representation of the course of an episode of breakthrough cancer pain which was treated with Abstral, and was also consistent with the SPC.

ProStrakan submitted that this perspective was supported by official guidance and expert opinion. Cephalon objected to claims that Abstral had onset of effect 'in minutes' on the grounds that this suggested a rapid speed of onset of pain relief. In fact this was appropriate. Guidance from the Medicines and Healthcare product Regulatory Agency (MHRA) on the use of 'fast-acting' claims stated that onset of effect of 30 minutes would be required to support a claim of 'fast-acting' for products such as those for acute pain relief or hayfever treatments. Abstral's onset of effect was well within this time period and so the product could be regarded as fast-acting. Recommendations on management of breakthrough cancer pain stated that treatment should have a rapid onset of effect seen 'within minutes' (Bennett *et al* 1998, Coluzzi *et al* 1998).

Clinicians had historically used immediate release oral opioids in the management of breakthrough cancer pain and they continued to be the mainstay of treatment; their onset of effect was 20-30 minutes (Davies *et al* 2009). Given that Abstral worked from 15 minutes it seemed reasonable to describe it in terms that were consistent with a faster onset of action than standard treatment.

ProStrakan was very concerned about the allegation of a breach of the undertaking given in Case AUTH/2207/2/09. ProStrakan took compliance with the Code extremely seriously and quickly sought guidance from the PMCPA when the accusation of a breach of undertaking was first made by Cephalon. In line with the undertaking, ProStrakan discontinued use of all materials containing the claim ruled in breach or similar claims with effect from 13 March 2009. All sales and marketing materials containing the claim at issue or similar claims were withdrawn. When developing new materials ProStrakan was anxious to ensure that it described the onset of effect of Abstral, which was an important feature in the management of breakthrough pain, in a manner which was both helpful to prescribers and consistent with the SPC. ProStrakan submitted that its current campaign respected its undertaking and was therefore not in breach of Clause 25. Through its actions, which had been prompt and thorough, it had maintained high standards and had not brought discredit on the industry; ProStrakan did not believe that it had breached Clauses 9.1 or 2 of the Code.

PANEL RULING

The Panel noted that Section 5.1 of the Abstral SPC (Pharmacodynamic properties) stated that '…Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards…'. Section 4.2 of the SPC (Posology and method of administration) stated that 'if adequate analgesia is not obtained within 15-30 minutes of administration of a single sublingual tablet, a second 100 microgram sublingual tablet may be administered'.

In the previous case, Case AUTH/2207/2/09, the Panel noted that the claim at issue 'Rapid relief of breakthrough cancer pain from 10 minutes' was based upon the efficacy data from study EN3267-005. Nonetheless the Panel considered that the ten minute claim was inconsistent with the particulars listed in the Abstral SPC and a breach of Clause 3.2 of the Code was ruled.

The claims now at issue in Case AUTH/2235/5/09 were 'To hell and back in minutes' and that Abstral 'Acts in minutes'. In the Panel's view most readers would not consider 'in minutes' to be as long as the 15 minutes referred to at Section 5.1 of the SPC; some readers might even consider 'in minutes' to mean less than 10. The advertisement featured three faces of a women showing how her expression changed as she experienced pain relief. The Panel also noted that 'Acts in minutes' was preceded by 'Dissolves in seconds' so the claim in full read 'Dissolves in seconds. Acts in minutes'. In the Panel's view the depiction of only three faces and the accompanying claim 'Dissolves in seconds' added to the impression that Abstral acted very quickly. The Abstral SPC was quite specific with regard to timings whereas the advertisement left it to the reader's judgement to decide what 'in minutes' meant. This was unacceptable. Time to onset of action was particularly relevant for a medicine to treat breakthrough cancer pain; it was unhelpful not to give more details. The Panel

considered ProStrakan's submission that the claim was consistent with the SPC because it used the same units of time disingenuous. The Panel considered that by not giving more information as to the time that Abstral took to act, the claims 'Acts in minutes' and 'To hell and back in minutes' were misleading and a breach of Clause 7.2 was ruled. The Panel also considered that each unqualified claim was inconsistent with the particulars listed in the SPC in that most readers would assume that Abstral took less than 15 minutes to act. A breach of Clause 3.2 was ruled.

The Panel noted that whilst the material in question was different to that considered in Case AUTH/2207/2/09, the issue was whether it was caught by the undertaking previously given. The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the claim in Case AUTH/2207/2/09, that Abstral gave relief of pain 'from 10 minutes', gave a quicker time to action for the product than stated in the SPC. It was alleged that the claim implied a statistical significance which was inconsistent with the SPC. The Panel had noted the efficacy data but considered nonetheless that the claim was inconsistent with the SPC. The Panel considered that although there were some differences between the two cases the unqualified claims now at issue, 'To hell and back in minutes' and that Abstral 'Acts in minutes', also implied a quicker time to action than stated in the SPC. The Panel further considered that the claims appeared to show a complete disregard for the previous ruling and were sufficiently similar such that they were covered by the undertaking given in that case. A breach of Clause 25 was ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel considered that the failure to comply with the undertaking reduced confidence in and brought discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned that new material had been developed which might imply to some readers an even quicker time to action than the 10 minute claim previously ruled in breach of the Code. The Panel considered that the failure to comply with the undertaking together with the exacerbation of effect, warranted reporting the company to the Code of Practice Appeal Board for it to consider the matter in accordance with Paragraph 8.2 of the Constitution and Procedure.

During the consideration of this case the Panel noted ProStrakan's submission regarding the MHRA's guidance on the use of 'fast-acting' claims. The MHRA noted that claims for fast relief of symptoms would be relevant for products for acute pain relief and hay fever. A rule of thumb for hay fever products would require onset of relief within about 30 minutes to support a 'fast-acting' claim. No time to onset of relief was stated for analgesics. The Panel was concerned that ProStrakan had misrepresented the MHRA guidance in this regard and requested that the company be so advised.

PROSTRAKAN'S COMMENTS ON THE REPORT

ProStrakan regretted the breach of the Code to which the current case related. Data from a new study showing onset of effect in ten minutes for Abstral had been included in the European promotional campaign and had been successfully defended in at least one other EU country. A UK advertisement containing this claim was derived from the European materials. This advertisement was reviewed, approved and certified through ProStrakan's copy approval system. As ProStrakan had acknowledged, the claim of ten minute onset was inconsistent with the fifteen minutes specified in the pharmacodynamics section of the SPC, in breach of Clause 3.2 (Case AUTH/2207/2/09).

When ProStrakan received the outcome of Case AUTH/2207/2/09 it was reviewed by senior management and the approval team. Once ProStrakan understood the nature of the error it was clear that it had no grounds for appeal and the approval team immediately identified, withdrew and reissued all materials containing the ten minute claim. This was a demanding piece of work for a small team in order to complete all activities within the five day time period required in the undertaking.

ProStrakan explained that in developing new materials the team considered a number of alternative options to describe Abstral's speed of onset. Breakthrough cancer pain was an area where prompt onset of pain relief was particularly important to patients. Prescribers needed to understand the profile of the various options for cancer pain management in order to match the appropriate medicine and formulation to the correct indication. Abstral materials had previously used the claims 'To hell and back in minutes' and 'Acts in minutes' and the approval team considered that these claims were a good representation of the profile of the product and were approvable for use in the UK. They specifically considered the important issue of whether these claims were in breach of the undertaking already given and concluded (on the basis of the arguments given in ProStrakan's response to the Panel) that they were not. As a result these claims were not removed from the original materials. This was a very serious error of judgement which had resulted in significant financial costs to the company from withdrawing and revising material again and, more importantly, a potential loss of reputation.

ProStrakan understood why the Panel considered

that the argument used to support the claims was disingenuous. However, the approval team had concluded that 'in minutes' was a true reflection of the onset of effect and it would not be understood by target customers to mean less than fifteen minutes. This genuinely held perspective was not morally fraudulent but it was naïve. The group had clearly failed to consider the effect of the advertisement as a whole or the risk that not only might readers consider 'in minutes' to mean something less than fifteen minutes, but that they might also consider it to mean less than ten minutes.

ProStrakan submitted that when it received the complaint from Cephalon the approval team sought advice from the Authority on the complaint and the procedure for seeking conciliation. The offer of conciliation was driven by a conviction that the claims and arguments were sound and that an independent third party would come to the same conclusion. To many people this view might be difficult to comprehend. In the Panel's view most readers would understand 'in minutes' as meaning something less than fifteen minutes; in this respect the approval team appeared to have represented a minority of readers (the target audience of prescribers for breakthrough cancer pain), but it failed to recognise this. As atypical readers coming to the piece with pre-conceived ideas their views were not necessarily those of a customer.

ProStrakan submitted that very regrettably, the outcome of this unchallenged 'group think' approach was an advertisement in the BMJ which suggested to some readers that Abstral had an onset of effect of less than 10 minutes and appeared to indicate a complete disregard for the previous ruling, as the Panel had described. However, the approval team had confirmed that it believed that it had taken the previous ruling carefully into account when devising the new claims; no-one had seen the potential for some readers to understand 'in minutes' as 'a few minutes'. In reality this was not 'complete disregard'; the team understood that the undertaking was a serious matter and it believed it had considered it, but its thinking was blinkered, self-censored and fell a long way short of the required rigour.

The Panel's concerns about the company's approach to the regulations appeared to have been compounded by its concern that ProStrakan had misrepresented the MHRA's advice about fast-acting claims. This was not ProStrakan's intention. The wording used was a clumsy attempt to summarise guidance which it believed was relevant to this complaint. ProStrakan acknowledged that the MHRA guidance stated that the timing was dependent on the indication and that the 30 minutes was specifically mentioned in relation to hayfever and regretted not having made this clearer.

ProStrakan submitted that this case constituted a 'critical incident' in terms of its review and approval processes and the company had reviewed it as such. Both the current and previous case arose from errors of interpretation and judgement due to inwardly focused and insufficiently rigorous thinking within an insulated and highly cohesive group. ProStrakan did not believe there was a systemic failure in its processes; all materials were carefully reviewed and certified through its electronic approval system. ProStrakan's action plan to reduce the risk of such an event happening again was as follows:

a) Once the case was published the general manager would provide details of it to all employees and reinforce the importance of a Code compliant culture throughout the company.

b) All staff and contractors involved with preparation, review and certification of UK and European materials would undergo Code refresher training by 1 October 2009.

c) Sales and marketing teams would be informed about relevant published Code cases with regular review at monthly team meeting.

d) Roles and responsibilities within approval teams would be changed to promote critical evaluation, specifically:

- Development of an 'Approval team charter' to encourage expression of dissenting views, thorough review of alternative approaches and formal consideration of risks of preferred choice
- External consultant to review all UK materials.

e) External consultant (Code compliance expert) engaged to thoroughly review company Code culture, policies and processes.

ProStrakan submitted that these actions would promote the importance with which it regarded the Code throughout the company, improve the quality of its approval processes and reduce the risk of future breaches.

In line with the undertaking ProStrakan had critically evaluated all Abstral promotional materials and had removed any material which could imply an onset of action of less than fifteen minutes. In order to improve objectivity these materials had also been reviewed by an external consultant.

In conclusion, ProStrakan submitted that the comments above were not intended to justify or mitigate its actions and decisions; the comments represented the outcome of an internal review carried out in order to understand what went wrong and prevent reoccurrence. ProStrakan fully appreciated the severity of these matters and greatly regretted that its action had brought discredit on the industry.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that the advertisement at issue had been used since January 2009 when Abstral was launched in the UK. The advertisement's date of preparation, March 2009, indicated when it had been re-approved following ProStrakan's review of material pursuant to the undertaking given in Case AUTH/2207/2/09. The Appeal Board was concerned that senior managers within the company had considered that the advertisement now at issue was acceptable given the outcome of the previous case.

The Appeal Board noted that as a result of the rulings in this case, Case AUTH/2235/5/09, ProStrakan had instigated a major review of its compliance policies and procedures which was due to be completed by December 2009. The Appeal Board noted ProStrakan's submission that it had strengthened its approval system with the addition of experienced consultants and this would be ongoing.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of ProStrakan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in six months' time when ProStrakan's compliance review would be complete. On receipt of the 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.

APPEAL BOARD FURTHER CONSIDERATION

The audit was conducted in January 2010. The Appeal Board noted that although ProStrakan had improved its processes, procedures and skills there were, nonetheless, still some areas which needed further attention. The Appeal Board decided that ProStrakan should be reaudited. On receipt of the reaudit report the Appeal Board would consider whether further sanctions were necessary.

The reaudit was conducted in July 2010. The Appeal Board considered that progress had been made since the previous audit. The company had plans to ensure maintenance or further improvement of standards. The Appeal Board decided that no further action was required.

Complaint received	**28 May 2009**
Undertaking received	**3 July 2009**
Appeal Board Consideration	**23 July 2009, 24 February 2010, 22 July 2010**
Interim Case Report published	**26 August 2009**
Case completed	**22 July 2010**

JOURNALIST, MEMBER OF THE PUBLIC and EX-EMPLOYEE v ASTRAZENECA

Promotion of Seroquel

Three complaints were received about the promotion of Seroquel (quetiapine) by AstraZeneca in the UK.

In Case AUTH/2294/1/10 a journalist alleged that a Seroquel advertisement in the British Journal of Psychiatry, April 2004 featured a claim for 'no weight gain', long after AstraZeneca was aware of precisely such effects.

In Case AUTH/2296/1/10 a member of the public asked the Authority to review an online BBC news item, 'Firm "suppressed" drug test data', published 26 January 2010 in relation to the Code.

The news item stated that a former medical adviser for Seroquel was pressurised to approve promotional material which stated that weight gain was not an issue. The medical adviser stated that clinical data available when Seroquel was launched showed patients gained statistically and clinically significant weight. The medical adviser further stated that he was put under quite significant pressure to sign off claims with regard to lack of weight gain and he was unwilling to sign that off. The news item stated that in the US Seroquel was marketed with claims that it would not cause weight gain. That was not done in the UK except for one advertisement published in the British Journal of Psychiatry, April 2004.

In Case AUTH/2297/1/10 an ex-employee of AstraZeneca referred to a Radio 4 documentary, File on 4, broadcast on Tuesday, 26 January 2010, which criticised promotional claims for Seroquel. In particular the complainant referred to an advertisement which was published in the British Journal of Psychiatry, 2004. The complainant provided a web-link to the File on 4 programme and also to articles in the Washington Post, 18 March 2009, and New York Times, 29 October 2009. The complainant stated that the links were provided to assist in the investigation.

The detailed response from AstraZeneca is given below. The cases were considered under the 2003 Code using the 2008 Constitution and Procedure.

In Case AUTH/2294/1/10 the Panel noted that the Seroquel advertisement at issue featured the claim 'The only atypical with placebo level EPS [extra-pyramidal symptoms] (including akathisia) and placebo level prolactin concentrations and a favourable weight profile across the full dose range'. The Panel thus considered that the claim in full sought to establish Seroquel as an atypical antipsychotic which was distinctly different to the others in the class in that it was the only one to have placebo level EPS, placebo level prolactin concentrations and a favourable weight profile across the full range.

The Panel noted that in the absence of any explanation it was left to the readers' judgement as to what was meant by a 'favourable weight profile'. The Panel noted that Allison *et al* (1999) had estimated and compared the effects of antipsychotics (both conventional and atypical) on bodyweight and concluded that all were associated with weight gain. Among the atypical agents the mean increases in weight were 4.55kg (clozapine), 4.15kg (olanzapine), 2.92kg (sertindole), 2.1kg (risperidone) and 0.04kg (ziprasidone). The mean increase in weight with Seroquel was not calculated due to lack of data.

The Panel considered that if all of the other atypical antipsychotics were known to cause weight gain then it was not unreasonable for readers to assume that if Seroquel was 'The only atypical with … a favourable weight profile across the full dose range' then it might be an atypical with no effect on bodyweight. This was not so. Arvanitis and Rak (1997) reported that the mean increase in weight was 2.2kg (n=1085). (Allison *et al* had reported that the mean increase in weight for risperidone was 2.1kg and 2.92kg for sertindole). Across the dose range for Seroquel, 75/150/300/600/750mg daily, the mean increase in weight was 0.9/2.9/2.0/2.6/2.3kg respectively. Jones and Huizar (2003) reported a mean increase in weight of 1.8kg with Seroquel therapy. Brecher *et al* (2000) reported on the long-term weight changes in 427 patients over 18 months. Weight change differed over time from -1.53kg after weeks 40-52 (n=41) to +1.94kg after weeks 53-78.

The Panel noted that the relevant Seroquel SPC listed weight gain as a common (≥1% - <10%) adverse event which occurred predominantly during the early weeks of therapy.

Overall the Panel considered that the advertisement was misleading with regard to the effect on bodyweight that would be expected with Seroquel therapy compared with the other atypical medicines. Although the advertisement did not state 'no weight gain' as alleged it sought to differentiate Seroquel from other medicines in the class in that it was the only one with a 'favourable weight profile across the full dose range'. Given that the other medicines caused weight gain, the

advertisement could be read as implying that Seroquel did not. This was not so. Similarly, the advertisement could be read as implying that Seroquel had a clear advantage regarding its 'favourable weight profile …' and this was not supported by the data submitted by AstraZeneca. The claim 'The only atypical with … a favourable weight profile…' was thus misleading and could not be substantiated. Breaches of the Code were ruled.

In Case AUTH/2296/1/10 the Panel considered that its rulings above in Case AUTH/2294/1/10 applied here also. The Panel further considered that, given the data, high standards had not been maintained. A breach the Code was ruled.

Misleading prescribers about a potential side-effect of therapy could prejudice patient safety and was of an activity likely to be in breach of Clause 2. On balance, however, the Panel considered that the circumstances were not such as to warrant a ruling of a breach of that clause which was reserved as a sign of particular censure. No breach of Clause 2 was ruled.

In Case AUTH/2297/1/10 the Panel only considered allegations regarding material used in the UK. The Panel considered that its rulings above in Cases AUTH/2294/1/10 and AUTH/2296/1/10 applied here also. The complainant in this case unsuccessfully appealed the Panel's ruling of no breach of Clause 2.

Three complaints were received about the promotion of Seroquel (quetiapine) by AstraZeneca in the UK.

Case AUTH/2294/1/10

COMPLAINT

A journalist referred to a Seroquel advertisement (ref 01/03/13526/A), placed by AstraZeneca UK Limited in the British Journal of Psychiatry, April 2004. The complainant alleged that the advertisement featured a claim for 'no weight gain', long after AstraZeneca was aware of precisely such effects.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 7.2, 7.4 and 7.9 of the 2003 Code.

Case AUTH/2296/1/10

COMPLAINT

A member of the public brought to the Authority's attention an online BBC news item, 'Firm "suppressed" drug test data', published 26 January 2010. The complainant asked the Authority to review the item in relation to the Code.

The news item stated that a former medical adviser for Seroquel was pressurised to approve promotional material which stated that weight gain was not an issue. The medical adviser stated that clinical data available when Seroquel was launched showed patients developed significant weight gain, significant both statistically and clinically. The medical adviser further stated that he was put under quite significant pressure to sign off claims with regard to lack of weight gain and he was unwilling to sign that off. The news item stated that in the US Seroquel was marketed with claims that it would not cause weight gain. That was not done in the UK except for one advertisement published in the British Journal of Psychiatry, April 2004.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.4, 7.9 and 9.1 of the 2003 Code.

Case AUTH/2297/1/10

COMPLAINT

An ex-employee of AstraZeneca referred to a Radio 4 documentary, File on 4, broadcast on Tuesday, 26 January 2010, which criticised promotional claims for Seroquel. In particular the complainant referred to an advertisement published in the British Journal of Psychiatry, 2004. The complainant provided a web-link to the File on 4 programme and also to articles in the Washington Post, 18 March 2009, and New York Times, 29 October 2009. The complainant stated that the links were provided to assist in the investigation.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.4, 7.9 and 9.1 of the 2003 Code.

* * * * *

The three cases above were considered under the 2008 Constitution and Procedure.

* * * * *

Cases AUTH/2294/1/10 and AUTH/2297/1/10

RESPONSE

AstraZeneca submitted that the Seroquel advertisement was directed to UK health professionals only; the target audience was psychiatrists and claims included in the advertisement should be considered in that context. AstraZeneca could not understand how the complainant in Case AUTH/2294/1/10 could contend that the advertisement claimed 'no weight gain' when it actually stated '… a favourable weight profile across the full dose range' and also listed weight gain as common in the prescribing information.

Health professionals would take from this advertisement that weight gain was associated with

Seroquel and that the profile was favourable given the available data at the time on Seroquel and in the context of the overall class of atypical antipsychotics. The Oxford English dictionary defined favourable as 'satisfactory', and profile as 'an outline of something'. This interpretation was consistent with the prescribing information which listed weight gain as common. This did not imply that there was no weight gain with Seroquel nor did it downplay the weight profile of Seroquel. As such, AstraZeneca strongly refuted any breach of Clause 7.9 of the 2003 Code.

One of the references used to support the claim, 'a favourable weight profile across the full dose range', was a primary registration study for Seroquel in the acute treatment of schizophrenia (Arvanitis and Rak, 1997). In this double-blind, randomised study, efficacy and tolerability (including weight gain) were examined across five fixed doses of Seroquel (75/150/300/600/750mg daily), compared with haloperidol and placebo in patients with acute schizophrenia. The mean increases in weight observed with Seroquel, from low to high dose, were 0.9/2.9/2.0/2.6/2.3kg, respectively. This was clearly consistent with the claim 'a favourable weight profile across the full dose range'. This was also consistent in the context of the wider data at the time: a meta-analysis conducted a few years previously found an estimated mean weight gain change with the new antipsychotics of 4.45kg (clozapine), 4.15kg (olanzapine), 2.92kg (sertindole), 2.1kg (risperidone) and 0.04kg (ziprasidone) after 10 weeks (Allison *et al*, 1999). While Seroquel was not included in that meta-analysis because insufficient data were available at the time, the weight changes observed with other atypical antipsychotics were predominantly greater than those observed for Seroquel by Arvanitis and Rak. AstraZeneca therefore considered that the claim about a favourable weight profile was a fair and balanced reflection of the overall evidence relating to weight change associated with atypical usage at the time. As such, the company denied any breach of Clauses 7.2, 7.4 and 7.9.

Jones and Huizar (2003) cited in the advertisement, also supported the claim. In this pooled analysis of two 12-week randomised, double-blind studies of Seroquel, in bipolar mania, the mean weight change from baseline in the Seroquel arm was 1.8kg, compared with –0.2kg in the placebo arm (n=604). While 9.1% of patients reported weight gain as an adverse event in the quetiapine arm, compared with 1.5% in the placebo arm, none withdrew from the study due to weight gain. The mean weight gain observed in this 12-week study relative to that observed in Allison *et al* at 10 weeks, again supported the claim of a favourable weight profile for Seroquel.

Such a weight profile was an important consideration for health professionals, as the clinical significance of weight gain must also be considered against long-term treatment data (Brecher *et al*, 2000).

Brecher *et al*, which was cited in the advertisement at issue, also substantiated the weight profile claim. This study assessed the long-term weight changes (from 6 weeks to beyond 18 months) observed in a cohort of 427 patients with schizophrenia in a review of controlled and uncontrolled clinical trials of Seroquel and respective open-label extensions (patients received a mean dose of 475mg/day after one year of open-label treatment). The mean weight change from baseline was +1.58kg after 9-13 weeks (n=170), +0.26kg after 14-26 weeks (n=165), +1.66kg after 27-39 weeks (n=134), -1.53kg after 40-52 weeks (n=41) and +1.94kg after 53-78 weeks (n=146).

In the same study, weight changes in relation to baseline body mass index (BMI) were analysed in 178 patients from patients who had received Seroquel therapy long-term for at least 6 months (mean duration 18.6 months). BMI was widely accepted as a measure of weight change and classification, since it described relative weight for height (WHO, 1998). Brecher *et al* reported a tendency towards weight gain in those with low pre-treatment BMI, and towards weight loss in those with high pre-treatment BMI. Additionally, the 95% confidence intervals for the mean change in weight overlapped zero in the group as a whole and in all subgroups except the severely obese (BMI≥35kg/m², n=14) in whom slight weight loss was observed. AstraZeneca thus regarded the above data supported the favourable weight profile claim used in the advertisement.

With regard to the claim at issue, Brecher *et al* reported the mean change in weight for each of three dosage groups (≤300mg, >300-≤500mg and >500mg/day). Using the modal dose value for the last recorded weight value, these longitudinal data and associated confidence intervals showed no effect of Seroquel on weight at any dose, and there was no correlation between increasing dose and mean long-term weight changes. AstraZeneca considered this data strongly supported the claim, 'favourable weight profile across the full dose range'. Indeed, the authors stated: 'Quetiapine appeared to have a weight neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI <18.5 kg/m²) and severely obese patients (BMI> 35 kg/m²)'.

AstraZeneca noted that the articles in the Washington Post and New York Times, referred to by the complainant in Case AUTH/2297/1/10, were published by lay journalists in US newspapers for a US audience and did not represent a scientific analysis of the Seroquel trial data.

In summary, AstraZeneca considered that the advertisement was a fair and balanced reflection of the overall evidence at the time relating to Seroquel and more broadly, relating to weight change associated with atypical usage.

AstraZeneca submitted that weight gain was listed as common, with the corresponding footnote: 'Occurs predominantly during the early weeks of

treatment', in the October 2003 SPC which was current when the advertisement at issue was published in 2004. Indeed, the SPC had referred to weight gain since the product was first marketed. At launch, the UK label listed weight gain as an adverse event, occurring in 2% of patients on Seroquel, compared with 0% of patients on placebo. 'Increased appetite' was first listed (as a common undesirable effect) on the SPC dated 9 September 2009.

In summary, AstraZeneca strongly refuted the allegation in Case AUTH/2294/1/10 that the advertisement claimed no weight gain with Seroquel long after the company was aware of precisely such effects. As such, AstraZeneca did not consider that the advertisement had breached Clauses 7.2, 7.4 and 7.9 of the 2003 Code. Similarly in Case AUTH/2297/1/10, AstraZeneca denied breaches of Clauses 7.2, 7.4 and 7.9 of the 2003 Code. Further, taking into account the points outlined above and that the advertisement was published in a journal directed at a specialist audience, AstraZeneca disagreed that it had not maintained high standards or could be considered to have brought discredit upon or reduced confidence in the pharmaceutical industry. The company denied breaches of Clauses 9.1 and 2 of the Code.

Case AUTH/2296/1/10

RESPONSE

AstraZeneca noted that the complainant asked the Authority to review the BBC news item in relation to the Code. No complaint was alleged.

AstraZeneca noted that the news item, which was an online summary of a Radio 4 news programme and the File on 4 programme, that was first broadcast on 26 January 2010, only referred to one claim from a single UK promotional item: an advertisement for Seroquel in the April 2004 edition of the British Journal of Psychiatry. This advertisement included a claim 'favourable weight profile across the full dose range'.

AstraZeneca further noted that the Authority had referred to a quotation from its former medical adviser for the Radio 4 programme referring to the certification of 'claims with regard to the lack of weight gain'. However, in the programme the medical adviser further stated that he was 'unwilling to sign that off'. Therefore, AstraZeneca did not understand why the Authority had asked it to respond in relation to all relevant Seroquel material used with UK health professionals in addition to the British Journal of Psychiatry advertisement mentioned above.

AstraZeneca submitted that it did not currently use any marketing materials which stated a 'lack of weight gain' for Seroquel. However, for a product that had been marketed for more than 12 years in the UK, the company did not believe that it could reasonably investigate and respond to such a broad request in relation to specific clauses of the Code.

AstraZeneca restated that weight gain was listed as common in the October 2003 SPC which was current when the 2004 advertisement was published. Indeed, the SPC had referenced weight gain since the product was first marketed. As regards increased appetite, this was first listed (as a common undesirable effect) on the SPC of 9 September 2009. The relevant SPCs were provided and reflected all such listings and modifications according to relevant regulatory guidance and processes.

Case AUTH/2294/1/10

PANEL RULING

The Panel noted that the Seroquel advertisement at issue featured the claim 'The only atypical with placebo level EPS [extra-pyramidal symptoms] (including akathisia) and placebo level prolactin concentrations and a favourable weight profile across the full dose range'. The Panel thus considered that the claim in full sought to establish Seroquel as an atypical antipsychotic which was distinctly different to the others in the class in that it was the only one to have placebo level EPS, placebo level prolactin concentrations *and* a favourable weight profile across the full range.

The Panel noted that in the absence of any explanation it was left to the readers' judgement as to what was meant by a 'favourable weight profile'. The Panel noted that Allison *et al* had estimated and compared the effects of antipsychotics (both conventional and atypical) on bodyweight. The authors concluded that all of the antipsychotics examined were associated with weight gain. Among the atypical agents the mean increases in weight were 4.55kg (clozapine), 4.15kg (olanzapine), 2.92kg (sertindole), 2.1kg (risperidone) and 0.04kg (ziprasidone). The mean increase in weight with Seroquel was not calculated due to lack of data.

The Panel considered that if all of the other atypical antipsychotics were known to cause weight gain then it was not unreasonable for readers to assume that if Seroquel was 'The only atypical with … a favourable weight profile across the full dose range' then it might be an atypical with no effect on bodyweight. This was not so. Arvanitis and Rak reported that the mean increase in weight was 2.2kg (n=1085). (Allison *et al* had reported that the mean increase in weight for risperidone was 2.1kg and 2.92kg for sertindole). Across the dose range for Seroquel, 75/150/300/600/750mg daily, the mean increase in weight was 0.9/2.9/2.0/2.6/2.3kg respectively. Jones and Huizar reported a mean increase in weight of 1.8kg with Seroquel therapy. Brecher *et al* reported on the long-term weight changes in 427 patients over 18 months. Weight change

differed over time from -1.53kg after weeks 40-52 (n=41) to +1.94kg after weeks 53-78.

The Panel noted that the relevant Seroquel SPC listed weight gain as a common (≥1% - <10%) adverse event which occurred predominantly during the early weeks of therapy.

Overall the Panel considered that the advertisement was misleading with regard to the effect on bodyweight that would be expected to be observed with Seroquel therapy compared with the other atypical medicines. Although the advertisement did not state 'no weight gain' as alleged it sought to differentiate Seroquel from other medicines in the class in that it was the only one with a 'favourable weight profile across the full dose range'. Given that the other medicines caused weight gain, the advertisement could be read as implying that Seroquel did not. This was not so. Similarly, the advertisement could be read as implying that Seroquel had a clear advantage regarding its 'favourable weight profile …' and this was not supported by the data submitted by AstraZeneca. The claim 'The only atypical with … a favourable weight profile…' was thus misleading and could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. The Panel considered that the claim did not reflect the evidence regarding the side-effect of weight gain. A breach of Clause 7.9 of the Code was ruled.

Case AUTH/2296/1/10

PANEL RULING

The Panel considered that its rulings above in Case AUTH/2294/1/10 of breaches of Clauses 7.2, 7.4 and 7.9 applied here also. The Panel further considered that, given the data, high standards had not been maintained. A breach of Clause 9.1 was ruled.

Misleading prescribers about a potential side-effect of therapy could prejudice patient safety and this was referred to in the supplementary information to Clause 2 as an example of an activity likely to be in breach of that clause. On balance, however, the Panel considered that the circumstances were not such as to warrant a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

Case AUTH/2297/1/10

PANEL RULING

The Panel only considered allegations regarding material used in the UK.

The Panel considered that its rulings above in Cases AUTH/2294/1/10 and AUTH/2296/1/10 applied here also.

The complainant in this case appealed the Panel's ruling of no breach of Clause 2.

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The Panel had considered the matter based on an email sent to complaints@pmcpa.org.uk and the links that appeared in that email. The Panel in error did not consider an almost identical email with additional attachments (including Spielmans and Parry, 2010) that was sent to the Director. Both emails and the attachments were provided to AstraZeneca together with the complainant's appeal.

* * * * *

APPEAL BY THE COMPLAINANT

The complainant noted that AstraZeneca had been unable to produce the certificate approving the advertisement from its archive. What proof, if any, did AstraZeneca have that it was ever approved?

The complainant noted that the Panel had failed to consider Spielmans and Parry (2010) due to an error for which it had apologized. Whilst the complainant encouraged the Appeal Board to read the whole paper, he referred particularly to pages 11 and 12 and the associated references.

The complainant noted that in an article in the online Pharmaceutical Journal, AstraZeneca had stated that 'In response to these complaints, AstraZeneca UK asserted to the PMCPA that it believed the content of the advertisement to be a fair and balanced reflection of the overall evidence relating to weight change associated with atypical usage at the time concerned. Given the historical nature of the complaint, AstraZeneca UK will not appeal the decision'.

The complainant questioned if AstraZeneca had accepted the Panel's decision and alleged a breach of Clause 2.

COMMENTS FROM ASTRAZENECA

AstraZeneca submitted that before it responded to the appeal, it had to first clarify the specific complaint that was the subject of the appeal. This clarification was important as significant additional information had been submitted by the complainant on appeal that was not relevant to the underlying complaint at issue.

AstraZeneca submitted that there was no clear articulation of a specific complaint. The complainant complained about promotional claims made for Seroquel as referenced in a recent File on 4 documentary first broadcast on BBC Radio 4 on 26 January 2010, but did not specify the particular claim that was the subject of his complaint. AstraZeneca noted that the only UK claim for

Seroquel referred to in this radio programme was one in an advertisement published in the British Journal of Psychiatry in April 2004, '…a favourable weight profile across the full dose range'. Therefore, the initial complaint now being appealed related only to that claim. The target audience of the advertisement in question was UK psychiatrists.

AstraZeneca did not agree with the complainant's contention that there was a breach of Clause 2. Clause 2 of the Code was reserved for cases in which activities or materials associated with promotion brought discredit upon, or reduced confidence in, the pharmaceutical industry; the supplementary information noted that a ruling of a breach of this clause was reserved as a sign of particular censure. This clause was not applicable in this case.

AstraZeneca did not agree that the complainant's reasons for appeal were valid and the rationale for this conclusion was set out below.

AstraZeneca noted that based on the subject of the underlying complaint (ie the challenged 2004 UK advertisement regarding '…a favourable weight profile across the full dose range' for Seroquel) the multiple enclosures and attachments submitted by the complainant as part of the appeal were not relevant. These irrelevant materials included:

- Spielmans and Parry and associated references
- Links to articles from the Washington Post and New York Times
- Internal AstraZeneca emails produced and used as exhibits in connection with the US litigation process

AstraZeneca noted that the complainant stated that the Panel had failed to consider Spielmans and Parry in its ruling due to an administrative error by the Authority. The complainant had requested that the Appeal Board consider Spielmans and Parry in relation to his appeal. To be clear, Spielmans and Parry provided a US context, and although the paper referenced Seroquel (among other medicines), the Seroquel references had no relationship to the advertisement at issue or to any alleged AstraZeneca practices. Therefore, AstraZeneca submitted that this paper was irrelevant and therefore not a valid reason for overturning the Panel's ruling of no breach of Clause 2. The content of the attached US news articles and internal emails likewise bore no relationship to the challenged 2004 UK advertisement and provided no basis for overturning the Panel's ruling.

The complainant also noted that AstraZeneca had been unable to produce the certificate approving the advertisement from its archive. As previously stated the certificate approving the advertisement was not available from the archive. Clause 14.6 stated 'Companies shall preserve certificates and the relevant accompanying information for not less than three years after the final use of the promotional material …'. The advertisement was last published over 5 years ago and the fact that the actual certificate was not available in the archive was not a substantive reason for overturning the Panel's ruling of no breach of Clause 2.

Finally, the complainant had also referred to a reactive statement provided by AstraZeneca to the Pharmaceutical Journal online. AstraZeneca submitted that this was made in response to public disclosure by a third party of a provisional Panel ruling in relation to one of three complaints above following on from the File on 4 programme. The complainant implied that such a statement indicated that AstraZeneca had not accepted the Panel's decision which was not the case. AstraZeneca had accepted the Panel's ruling. AstraZeneca did not understand how this reactive statement, which simply characterized AstraZeneca's initial position, was a reason for overturning the Panel's ruling of no breach of Clause 2.

AstraZeneca submitted that this case did not constitute a breach of Clause 2 as alleged. As previously stated, the 2003 Code stated a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances, which, as explained above, was not applicable in this case. Further, AstraZeneca contended that the complainant had failed to provide sufficient evidence to justify any reasonable grounds for appeal.

FINAL COMMENTS BY THE COMPLAINANT

The complainant stated that he was happy for the Appeal Board to review his comments, Spielmans and Parry and a transcript of the BBC File on 4 radio progamme (provided) and decide whether AstraZeneca had brought the industry into disrepute.

The complainant stated that from 1992 to 2001 he was employed by AstraZeneca Pharma UK and from 1995 to 2000 he was responsible for the medical aspects of the UK launch and subsequent marketing of Seroquel. The complainant alleged that when promotional materials were being prepared for the launch of Seroquel (September 1997) he was informed by a colleague that:

- certain members of the Seroquel headquarters team were attempting to coordinate the burying and manipulation of data to paint the product in a better light than the totality of the data suggested.
- That other members of the Seroquel headquarters team were being pressured and manipulated into aiding them.

A member of the Seroquel headquarters team had confirmed these allegations and provided more information. The complainant reported these allegations to his manager. They resolved to be

vigilant regarding the approval of marketing claims for Seroquel in the UK. This was done up until February 2000 when the complainant in effect left the company.

In the spring of 2009 the complainant became aware of a number of documents released onto the internet as part of class action lawsuits brought against AstraZeneca in the US regarding the promotion of Seroquel. These documents were usefully summarised in Spielmans and Parry.

APPEAL BOARD RULING

The Appeal Board noted that between 1997 and 2004 there was increasing evidence that weight gain was an issue with Seroquel. Spielmans and Parry reported that in July 2008 an internal analysis of quetiapine studies in schizophrenia conducted from 1993-1999, concluded that 'the incidence rate in adult patients with weight gain ≥7% in all trials was 18.2%'. In the 2004 SPC weight gain was listed as a common (≥1% - <10%) adverse event; in the 2009 SPC it was listed as a very common (>10%) event. There was also data to show that in terms of the amount of weight gained, Seroquel was no different to some other atypical antipsychotics. The Appeal Board was concerned that the claim 'The only atypical with placebo level EPS [extra-pyramidal symptoms] (including akathisia) and placebo level prolactin concentrations and a favourable weight profile across the full dose range' had favoured Seroquel in terms of its weight gain profile vs other atypical antipsychotics yet the evidence had not supported this.

The Appeal Board noted from the AstraZeneca representatives at the appeal that although the job bag for the advertisement at issue still existed, it did not contain the relevant certificate. The representatives stated that the company had not investigated how many times the advertisement at issue had been used or in which publications. The Appeal Board considered that generally it would be unusual for an advertisement to only be used once.

The Appeal Board was concerned about the lack of information provided by AstraZeneca about the generation of the advertisement at issue. It was also extremely concerned about email trails which implied that the company was keen not to disclose certain data. However, the Appeal Board noted that it was limited to making its decision based on activity in the UK and in that regard the advertisement at issue was the only one that had been specifically identified. The Appeal Board noted the Panel's ruling of breaches of the Code which had been accepted by AstraZeneca. The Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 and so it upheld the Panel's ruling of no breach of that clause. The appeal was thus unsuccessful.

	Complaint received	**Case completed**
Case AUTH/2294/1/10	**26 January 2010**	**12 March 2010**
Case AUTH/2296/1/10	**26 January 2010**	**12 March 2010**
Case AUTH/2297/1/10	**27 January 2010**	**19 May 2010**

CASE AUTH/2295/1/10

HOSPITAL CHIEF PHARMACIST v CEPHALON

Supply of Effentora

The chief pharmacist at an NHS trust complained about the provision of thirty boxes of Effentora (fentanyl citrate buccal tablets) by Cephalon. Effentora was indicated for the treatment of breakthrough pain (BTP) in adults with cancer who were already receiving maintenance opioid therapy for chronic cancer pain.

The complainant stated that a nurse working in the pain team had received from the goods receiving department thirty boxes of Effentora, a Schedule 2 controlled drug. All orders and deliveries of controlled drugs should be via the pharmacy department where auditable records were maintained in line with legal requirements.

This consignment had been initiated after a Cephalon representative met a local pain consultant. The consultant was unaware that her signature would be taken as an order, she thought she had only expressed an interest in the product.

Apart from serious breaches of UK regulations, which were being addressed elsewhere, the complainant alleged that this conduct breached the Code.

- ***No more than ten samples*** **– 30 boxes had been provided**
- ***Each sample must be marked*** **– Commercial packs with no other marking were provided**
- ***Narcotic drugs*** **– Effentora was a Schedule 2 controlled drug subject to ordering/storage and prescribing restrictions**
- ***Provision within hospitals must comply with hospital requirements*** **– The hospital requirements, supported by local guidelines, stated clearly that samples and free stock must not be left within the trust.**
- ***Supply as an inducement to prescribe*** **– The complainant attached emails which stated that Effentora was supplied as an inducement to prescribe and 'assist [Cephalon] with moving forward with a formulary application'.**

This was not the provision of stock since the consultant concerned was not authorized to purchase medicines on behalf of the trust and if they were for her private work they should not have been supplied to the trust.

There was significant risk in the company's conduct since this supply was not traceable and could easily have been misappropriated, also the supply was of short dated stock and patients might have inadvertently been given out-of-date medicines.

The detailed submission from Cephalon is given below.

The Panel noted that from the complaint it appeared that the consignment of Effentora was addressed such that it was delivered to a nurse in the pain team and not sent to the pharmacy department. The complainant also stated that the consultant was unaware that her signature would be taken as an order. In this regard the Panel noted that the request form provided by Cephalon headed 'Effentora Titration Stock Request' included a statement 'I can confirm that the above healthcare premises is licensed to receive and store controlled drugs and that the above named person is authorized to take delivery of the Effentora titration stock'. The form required the name of the person authorized to receive the delivery but not the signature of that person. The Panel queried whether the form in question had been signed as submitted by Cephalon given that the requesting consultant's name had been written in block capitals. The Panel noted that the person named as being authorized to receive delivery was not the person to whom the Effentora was delivered. There was no indication on the stock request form of exactly what had been requested or dispatched.

The Panel did not consider that the provision of Effentora met the definition of a sample as stated in the supplementary information to the Code. Further, Effentora was a Schedule 2 controlled drug and thus could not be provided as a sample. Thirty packs had been provided rather than the ten permitted for samples. The Panel did not consider that the packs provided were titration packs. The company had provided standard packs of the two lowest strengths of Effentora which it submitted were usually required to determine a patient's optimal dose. In the Panel's view a titration pack, as defined in the Code, was one pack which contained various strengths of a medicine, rather than standard packs of different strengths given for the purpose of titration. In the Panel's view the Effentora had been provided as free stock. The Panel ruled no breach of those clauses of the Code which related only to samples as defined in the Code.

The Panel noted the complainant's submission that the pain consultant was not authorized to order on behalf of the hospital trust and that the hospital requirements clearly stated that samples and free stock must not be left within the trust. This requirement was further supported by local guidelines. However the Panel noted that the

hospital guidelines provided by the complainant did not refer to free stock. The local document 'Working with the Pharmaceutical Industry' stated 'Samples should not be available for patients/carers, nor should any direct promotional activity, including providing details of direct supply activities be made available'. It was further stated that samples could be left with appropriate practitioners for personal use only. Such samples must not be used for patients. The arrangements reflected the requirements of the Code with regard to the need for a signed request and that no more than 10 samples could be provided in the course of a year. Appendix I of the document asked representatives to adhere to eight guidelines. It stated that samples could be left in pharmacy, and that no samples could be left with other trust staff. Samples must not be used in clinical practice without appropriate, prior authorization. The document 'Working with the Pharmaceutical Industry' referred to the basis upon which purchasing decisions should be made but did not identify who should make the decision. Contrary to the complainant's submission the Panel did not consider that the published hospital policy was clear about the provision of free stock. Samples were specifically mentioned; it was unclear as to what was envisaged by 'direct supply activities'. The Panel queried whether the trust's definition of 'sample' was the same as that given in the Code – particularly when, according to the trust, samples could not be used for patients. No specific mention was made in the trust guidelines about the supply of controlled medicines. Nonetheless the Panel considered that when providing free stock it was beholden upon the representative to make specific enquiries to ensure that its provision complied with hospital requirements irrespective of the status of the health professional involved. This was even more important when controlled drugs were being supplied. That the hospital guidelines did not mention free goods or the provision of controlled drugs did not mean that there were no relevant requirements. The Panel did not accept Cephalon's submission that it was entitled to rely on the status and knowledge of the relevant doctor. The provision of Effentora as free stock to the pain clinic did not comply with hospital requirements and thus a breach of the Code was ruled. This ruling was appealed by Cephalon.

The Appeal Board noted that the hospital guidelines included the term 'samples' but not the term 'free stock'. The term 'samples' had not been defined. The Appeal Board noted that the guidelines would have been written by hospital staff and in that regard it appeared that their use of the term 'samples' might not be the same as the use in the Code. It was possible that some hospital staff would view the term 'samples' as all embracing. Nonetheless it was not for the Appeal Board to second guess what the guidelines meant. The Appeal Board considered that as the hospital guidelines did not refer to 'free stock' the supply of Effentora could not have breached them. No breach of the Code was ruled.

The representative had facilitated the provision of free stock for a Schedule 2 controlled drug contrary to hospital requirements and had failed to maintain high standards in this regard. Breaches of the Code were ruled.

The Panel considered that the provision of a Schedule 2 controlled drug without sufficient controls fell short of competent care and brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled which was upheld on appeal by Cephalon.

The chief pharmacist at a NHS trust complained about the provision of thirty boxes of Effentora (fentanyl citrate buccal tablets) by Cephalon UK Limited. Effentora was indicated for the treatment of breakthrough pain (BTP) in adults with cancer who were already receiving maintenance opioid therapy for chronic cancer pain.

COMPLAINT

The complainant stated that the local hospital pharmacy department was contacted by a nurse working in the pain team at the trust concerned that she had received from the goods receiving department thirty boxes of Effentora, a Schedule 2 controlled drug subject to control under the Misuse of Drugs regulations. All orders and deliveries of controlled drugs should be via the pharmacy department where auditable records were maintained in line with legal requirements.

This consignment had been initiated after a visit by a Cephalon representative to a pain consultant within the trust. The consultant was unaware that her signature would be taken as an order – although she had no authority to place such an order on behalf of the trust – and thought that this was an expression of interest in the product.

Apart from serious breaches of the Misuse of Drugs regulations, which were being addressed elsewhere, the complainant alleged that this conduct breached Clause 17 of the Code.

- *17.2 No more than ten samples* – The consultant was provided with 30 boxes of the medicine
- *17.5 Each sample must be marked* – They were supplied as commercial stock in commercial packaging with no other marking
- *17.6 Narcotic drugs* – Effentora was a Schedule 2 controlled drug subject to ordering/storage and prescribing restrictions
- *17.8 Provision within hospitals must comply with hospital requirements* – The hospital requirements stated clearly that samples and free stock must not be left within the trust. This was further supported by the local guidelines (copies of each were provided)

- 17.12 *Supply as an inducement to prescribe* – The complainant attached emails which clearly stated that Effentora was supplied as an inducement to prescribe and 'assist [Cephalon] with moving forward with a formulary application'. This clearly contravened the hospital and local primary care trust (PCT) guidelines referred to above.

It could not be argued that this provision was stock as ordered since the consultant concerned was not authorized to purchase medicines on behalf of the trust and if the tablets were for her private work they should not have been supplied to the trust.

There was significant risk in the company's conduct since this supply was not traceable and could easily have been misappropriated and found its way onto the streets, also the supply was of short dated stock and the consultant might have inadvertently supplied out-of-date medicines to a patient.

As emails suggested that this was not a one-off incident, since it referred to 'another of these [free of charge] FOC Effentora orders', the complainant had told all chief pharmacists in the area and all members of the area purchasing consortium about her concerns.

When writing to Cephalon the Authority asked it to respond in relation to Clauses 2, 9.1 and 15.2 in addition to those clauses cited by the complainant.

RESPONSE

Cephalon stated that it had written to the complainant to apologise for what was an extremely unfortunate set of misunderstandings.

However, Cephalon noted that the consultant who completed the stock request form was not only an experienced consultant pain physician, familiar with the management requirements of controlled medicines, but was also the chair of the local medicines management committee and had signed the trust's guidelines for representatives. Given the physician's roles and experience the company considered this was an appropriately senior level of staff for the representative to have interacted with.

Clause 17 concerned the distribution of samples. The supplementary information to Clause 17 clearly identified a sample as a small supply of a medicine provided to health professionals so that they might familiarise themselves with it and acquire experience in dealing with it. The supplementary information further stated that titration packs, free goods and bonus stock provided to pharmacists and others were not samples and that titration packs were packs containing various strengths of a medicine for the purposes of establishing a patient on an effective dose.

Cephalon believed the complainant had misunderstood the nature of the stock provided to the hospital and the sub-clauses within the Code. While Cephalon did not wish to minimise the complainant's obvious concerns, it respectfully suggested that Clauses 17.2, 17.5 and 17.6 did not apply to titration stock and therefore denied any breach of these clauses.

The stock of Effentora requested by the pain consultant was solely for the purposes of titration and was provided free of charge in response to a signed request for titration stock. Effentora typically had to be titrated to the optimal maintenance dose. The packs were provided expressly for this purpose and not as samples for the purpose of familiarisation. Indeed, only the two lowest strengths of Effentora were provided which were usually required to determine an optimal dose for a given patient, there being five strengths in total.

However, the complainant made points that warranted further comment.

Cephalon recognised the concern that the consultant in question was unaware that her signature would be taken as an order. This was indeed an unfortunate situation; however, the company had made every attempt on the one-page form to indicate the situation clearly. The form was clearly entitled 'Effentora Titration Stock Request'. The person placing the order was required to indicate who was authorized to receive the delivery in the section 'Name of person authorized to receive the **delivery**:' (emphasis added). Immediately beneath the space for the name, telephone number and email address of the person authorized to receive delivery, was the statement 'Delivery on', thus again indicating that a delivery of stock was the outcome of completing the form. Finally, the lower half of the page required the person requesting the titration stock to complete the following declaration, 'I can confirm that the above healthcare premises is licensed to receive and store controlled drugs and that the person named above is authorized to take delivery of the Effentora titration stock'. The consultant signed and dated the form immediately beneath this statement.

Hence, the form signed was clearly not an expression of interest but an order form for titration stock.

Cephalon was aware of the controls on Schedule 2 medicines with regard to ordering and storage, which were the applicable elements here. With this consideration, following a small number of requests from health professionals for titration stock of Effentora, it was deemed necessary to have a formal titration stock request form to ensure appropriate control (a copy was provided). Any health professional that made a request then was obliged to complete obligatory information that highlighted and accounted for these restrictions. The consultant signed the form on which the location for delivery was stated.

The hospital requirements and locality guidelines

enclosed with the complaint were not clear that free stock was not to be left within the trust. However, the form ensured that the person and place nominated to receive the titration stock was authorized to do so. This aligned with any hospital policy that should be known by the requesting health professional. The consultant, as chair of the local medicines management committee, signed the guidelines regarding pharmaceutical representatives and could, therefore, reasonably be expected to be aware of all applicable policies within the trust including the individual hospital requirements regarding place of delivery of controlled medicines. Hence, Cephalon acted in good faith that the use of the request form by the requesting consultant was consistent with local guidelines.

With reference to the alleged breach of Clause 17.8, which referred to supply of medicines and samples complying with individual hospital requirements, Cephalon therefore took reasonable precautions regarding compliance with individual hospital requirements by gaining the consultant's prior approval and signature.

Cephalon regretted the circumstances of the complaint and the misunderstanding; however it believed it acted reasonably and in good faith and therefore asserted no breach of Clause 17.8.

With specific reference to the alleged breach of Clause 17.12, ie that the titration stock was supplied as an inducement to prescribe, the consultant made the request, as discussed above, and would be reasonably held accountable for appropriate supply of titration stock under hospital and local PCT guidelines, No sample was provided, rather, as clearly noted on the request form, titration stock was requested – a presentation of the two lowest strengths of Effentora that were usually required to place patients on a stable dose. The Effentora summary of product characteristics (SPC) made specific recommendations for the titration and use of specific tablet strengths, as part of risk management. Titration was required in all patients, and the consultant requested titration stock to assist in the initial administration to find a suitable maintenance dose for a very limited number of patients.

As the titration stock was clearly provided on request, it could not be held that supply was an inducement to prescribe. The request came from a person responsible, as chair of the local medicines management committee, for local hospital and PCT guidelines regarding formulary applications. There would still remain the stage of formal evaluation through a formulary submission that evaluated the evidence and other medicines that could also be used. There was no commitment by either the consultant or Cephalon to an ongoing supply of Effentora titration stock that could influence the recommendation by a formulary review panel.

In addition, the Appeal Board had previously ruled that an inducement must relate to the provision of an incentive for the individual (Case AUTH/2095/2/08). It was difficult to see what benefit the individual derived from the supply of titration to stock delivered to the hospital and therefore the company believed that it was not possible for any inducement to have occurred.

Cephalon therefore asserted that no sample was provided and no inducement to prescribe was present and therefore that there was no breach of Clause 17.12.

Based on the points made above, Cephalon believed it had acted to maintain high standards. Cephalon identified the need to produce a request form to ensure appropriate controls and gained a signature regarding supply and place of supply from a person who would reasonably be assumed to be aware of local trust policies and procedures regarding delivery of narcotic titration stock. Although Cephalon implemented appropriate controls as above, when it first became aware of the circumstances in this case it immediately suspended the ability for health professionals to request titration stock pending review of the process and resolution of this complaint. Cephalon also arranged for immediate removal of the titration stock from the hospital as requested by the pharmacy department. Cephalon denied a breach of Clause 9.1.

The representative involved had responded to a request from the health professional and was only involved in forwarding the form completed by the consultant to Cephalon head office, which arranged supply based on the details provided on the form. Cephalon took the information provided in good faith that it represented appropriate authorization to request and take delivery of the titration stock. The representative had interacted at the time with the same clinician who signed the pharmaceutical company representatives' guidelines for the trust. Cephalon denied a breach of Clause 15.2.

Overall, Cephalon believed that the availability of titration stock on the request of a limited number of health professionals was appropriate and was consistent with the titration steps required to use Effentora appropriately.

Given that Cephalon believed it had not therefore breached Clauses 9, 15 or 17 in that it reacted to a request for titration stock appropriately, did not provide a sample as an inducement to prescribe and acted on good faith following receipt of an order form signature from someone who would reasonably be assumed to be conversant with local trust policies, it did not believe that its actions had brought the industry into disrepute. Cephalon denied a breach of Clause 2.

With respect to the question regarding any documents sent with the titration stock, other than the logistics documentation, no further documentation was provided. The titration stock

contained the obligatory regulatory document within the box, such as the patient information leaflet. As requests for titration stock had been received via representatives, no briefing other than provision of a request form was considered necessary.

PANEL RULING

The Panel noted that from the complaint it appeared that the consignment of Effentora was addressed such that it was delivered to a nurse in the pain team and not sent to the pharmacy department. The complainant also stated that the consultant was unaware that her signature would be taken as an order. In this regard the Panel noted that the request form provided by Cephalon headed 'Effentora Titration Stock Request' included a statement 'I can confirm that the above healthcare premises is licensed to receive and store controlled drugs and that the above named person is authorized to take delivery of the Effentora titration stock'. The form required the name of the person authorized to receive the delivery but not the signature of that person. The Panel queried whether the form in question had been signed as submitted by Cephalon given that the requesting consultant's name had been written in block capitals. The Panel noted that the person named as being authorized to receive delivery was not the person to whom the consignment of Effentora was delivered. There was no indication on the stock request form of exactly what had been requested or dispatched.

The Panel noted that the complainant considered that the packs of Effentora had been provided as samples whilst Cephalon maintained that they were titration stock. The supplementary information to Clause 17, 'Definition of Sample', defined each term. A sample was a small supply of a medicine provided to health professionals so that they might familiarise themselves with it and acquire experience in dealing with it; titration packs were packs containing various strengths of a medicine for the purpose of establishing a patient on an effective dose.

The Panel did not consider that the provision of Effentora met the definition of a sample given in the Code. Further, Effentora was a Schedule 2 controlled drug and thus could not be provided as a sample under Clause 17.6. Thirty packs had been provided rather than the ten permitted for samples under Clause 17.2. The Panel did not consider that the packs provided were titration packs. The company had provided standard packs of the two lowest strengths of Effentora which it submitted were usually required to determine a patient's optimal dose. In the Panel's view a titration pack, as defined in the Code, was one pack which contained various strengths of a medicine, rather than standard packs of different strengths given for the purpose of titration. The Effentora SPC stated that the initial dose should be 100mcg titrating upwards as necessary. The product was available in a range of tablet strengths (100mcg-800mcg). In the Panel's view Cephalon had provided 30 packs of Effentora, a Schedule 2 controlled medicine, as free stock. The Panel ruled no breach of Clauses 17.2, 17.5 17.6, and 17.12 as these related to samples as defined in the Code.

The Panel noted the complainant's submission that the pain consultant was not authorized to order on behalf of the hospital trust and that the hospital requirements clearly stated that samples and free stock must not be left within the trust. This requirement was further supported by local guidelines. However the Panel noted that the hospital guidelines provided by the complainant did not refer to free stock. Representatives were reminded that the trust had a drugs guide and formulary. Promotional activities which conflicted with the recommendations of the formulary would not be tolerated. The local document 'Working with the Pharmaceutical Industry' stated 'Samples should not be available for patients/carers, nor should any direct promotional activity, including providing details of direct supply activities be made available'. It was further stated that samples could be left with appropriate practitioners for personal use only. Such samples must not be used for patients. The arrangements reflected the requirements of the Code with regard to the need for a signed request and that no more than 10 samples could be provided in the course of a year. Appendix I of the document asked representatives to adhere to eight guidelines. It stated that samples could be left in pharmacy, and that no samples could be left with other trust staff. Samples must not be used in clinical practice without appropriate, prior authorization. The document 'Working with the Pharmaceutical Industry' referred to the basis upon which purchasing decisions should be made but did not identify who should make the decision. Contrary to the complainant's submission the Panel did not consider that the published hospital policy was clear about the provision of free stock. Samples were specifically mentioned; it was unclear as to what was envisaged by 'direct supply activities'. The Panel queried whether the trust's definition of 'sample' was the same as that given in the Code – particularly when, according to the trust, samples could not be used for patients. No specific mention was made in the trust guidelines about the supply of controlled medicines. Nonetheless the Panel considered that when providing free stock it was beholden upon the representative to make specific enquiries to ensure that its provision complied with hospital requirements irrespective of the status of the health professional involved. This was even more important when controlled drugs were being supplied. That the hospital guidelines did not mention free goods or the provision of controlled drugs did not mean that there were no relevant requirements. The Panel did not accept Cephalon's submission that it was entitled to rely on the status and knowledge of the relevant doctor. In that regard the Panel noted that the document 'Working with the Pharmaceutical Industry' and its Appendix I appeared to have been signed off by someone other

than the consultant in question. The provision of Effentora as free stock to the pain clinic did not comply with hospital requirements and thus a breach of Clause 17.8 was ruled. This ruling was appealed.

The representative had facilitated the provision of free stock for a Schedule 2 controlled drug contrary to hospital requirements and had failed to maintain high standards in this regard. Breaches of Clauses 9.1 and 15.2 were ruled.

The Panel considered that the provision of a Schedule 2 controlled drug without sufficient controls fell short of competent care and brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

APPEAL BY CEPHALON

Cephalon submitted that the Panel's rulings in respect of Clauses 2 and 17.8 did not accurately reflect the factual circumstances in which Effentora was supplied to the pain clinic. As regards the breach of Clause 17.8, Cephalon was unclear as to which of the local guidelines it had breached.

Cephalon did not accept that there were serious breaches of the Misuse of Drugs regulations as alleged by the complainant. This had essentially underpinned the Panel's ruling of a breach of Clause 2.

Cephalon submitted that the legal basis for the supply and possession of controlled drugs in the UK was governed by the Misuse of Drugs Act 1971 Sections 4 and 5 of which established a general prohibition on the supply and possession of controlled drugs. Section 7 gave power to the Secretary of State to make secondary legislation. The regulations were made under Section 7 of the act and provided that the Secretary of State might issue licences authorizing the production, supply and possession of controlled drugs.

Cephalon noted that in this case, Effentora was manufactured in the US with the finished product being shipped to Cephalon's distributor in the UK. Distribution of Cephalon's branded products in the UK was subject to a distribution agreement and a technical agreement setting out the obligations of the contracting parties with particular reference to compliance with the applicable laws and regulations. In this case, the distributor was contractually required to keep written/electronic records sufficient to track the purchase and sale of product lots. In addition, it was required under the technical agreement to supply products to the approved sites and *bona fide* recipients of the products (see below).

Cephalon submitted that as regulation 10(1)(a) authorized registered medical practitioners to possess Schedule 2 controlled drugs for the purposes of their work, the hospital consultant was authorised to hold controlled drugs for the purposes of administering pain relief to patients in her care.

Cephalon submitted that regulation 14(2) provided that where a controlled drug was supplied otherwise than on a prescription or by way of administration by a practitioner (defined under Section 37 of the act to include a doctor) the supplier was permitted to supply the controlled drug if he had received a written requisition which:

- was signed by the person to whom the drug was supplied;
- stated the name, address and profession or occupation of the recipient; and
- specified the purpose for which the drug supplied was required and the total quantity to be supplied.

Cephalon noted the Effentora Titration Stock Request form was completed by the consultant, a senior physician in the hospital, and an authorized practitioner within the meaning of the act and the regulations to hold and administer controlled drugs. The consultant declared in the request form that the hospital was licensed to receive and store controlled drugs. As it was evident from the title of the request form, the requested supply of Effentora was intended for dose titration.

Cephalon submitted that although the quantity of Effentora was not expressly recorded on the request form, the other requirements set out in regulation 14(2) were essentially met. According to the representative's records the consultant had requested 10 boxes of 4 x 100 micrograms and 20 boxes of 4 x 200 micrograms of Effentora tablets for dose titration. A copy of the representative's notes and a signed witness statement from the representative was provided.

Whilst Cephalon accepted that there had been a technical breach of regulation 14, it did not accept that there were serious breaches of the regulations, as alleged by the complainant and included as part of the reasoning of rulings made by the Panel. This allegation would ordinarily mean that Cephalon had had no regard to the regulatory requirements for the supply of controlled drugs in the UK. This did not reflect the facts of this case.

Cephalon submitted that the Panel, however, correctly noted that the person authorized to receive the delivery of the Effentora titration stock the consultant was not the person to whom the consignment was actually delivered. As described above, following an agreement between Cephalon and its distributor, the distributor was solely responsible for the distribution of Cephalon's products to customers in response to orders placed by Cephalon's representatives. Regrettably, the distributor's failure to deliver the titration stock to the authorized practitioner, the consultant, was a breach of its obligations under that agreement.

Cephalon submitted that in this case, the intended recipient was clearly the consultant as an authorized practitioner under regulation 10(1)(a) and the named signatory on the request form as she would be undertaking the dose titration on her patients. Cephalon noted that although the consultant did not receive the titration stock herself, the delivery was received and signed for by a specialist nurse working in her offices.

Cephalon submitted that it had instructed its distributor to remove the titration stock from the hospital immediately on receipt of the complaint and that it was thoroughly investigating its breach of the applicable requirements. Cephalon submitted that it had acted responsively and responsibly in the course of the supply of a stock of Effentora to the consultant and the subsequent retrieval of the delivery from the hospital after the company was made aware of the complaint. Therefore, with the existing procedures and contractual arrangements in place for the distribution of Effentora in line with the current industry standards, Cephalon was troubled that these activities could properly and proportionately be characterised as bringing discredit upon or reducing confidence in the pharmaceutical industry in the context of Clause 2.

Cephalon submitted that the request form was intended for the ordering of titration stock only and it was not used for sample requests. Furthermore, supply of titration stock in response to a legitimate request made by a doctor to undertake dose titration, was consistent with the Effentora SPC Section 4.2 of which stated:

'Effentora should be individually titrated to an "effective" dose that provides adequate analgesia and minimises undesirable effects. In clinical studies, the effective dose of Effentora for BTP was not predictable from the daily maintenance dose of opioid. Patients should be carefully monitored until an effective dose is reached.

The initial dose of Effentora should be 100 micrograms, titrating upwards as necessary through the range of available tablets strengths ….

Method of titration

During titration, if adequate analgesia is not obtained within 30 minutes after the start of administration of a single tablet, a second Effentora tablet of the same strength may be used.

If treatment of a BTP episode requires more than one tablet, an increase in dose to the next higher available strength should be considered to treat the next BTP episode.

During titration, multiple tablets may be used: up to four 100 micrograms or up to four 200 micrograms tablets may be used to treat a single episode of BTP during dose titration according to the following schedule ...'

Cephalon submitted that the consultant requested a supply of the lowest two strengths of Effentora for dose titration in patients under her care (Sections 2 and 6.5 of the SPC referred). Five strengths of Effentora were authorized for supply to the UK market: 100; 200; 400; 600 and 800 micrograms. No specific titration pack (containing a smaller amount of tablets) was authorized under the terms of the existing Effentora marketing authorization. Indeed, the pack size provided (4 tablets per pack) was currently the only pack size commercially available in the UK. The amount supplied to the consultant would typically be sufficient to titrate four or five patients up to an effective maintenance dose for pain relief. Patients would generally be maintained at a higher strength than 200mcg per dose. However, the amount given to each patient during titration and maintenance was individualised according to that patient's clinical response as assessed by the treating physician. Cephalon supplied the approved pack size of Effentora as free stock for the specific purpose of dose titration, and not as samples, in response to the consultant's bona fide request for the same.

Cephalon submitted that the consultant was an experienced pain consultant familiar with the management requirements of controlled drugs; the medicines management committee chair; the clinician responsible for developing the Guidelines for drug company representatives; and was authorized under regulation 10(1)(a) to possess Schedule 2 controlled drugs for the purposes of administering pain relief to the patients under her control. In the circumstances, it appeared appropriate for Cephalon's representative to have met the consultant and processed her order for the requested Effentora titration stock.

Cephalon was unclear as to which hospital guidelines it had breached. Three documents had been provided. Cephalon submitted that although none of this guidance appeared to deal with the issue of free stock, it had respectfully asked the Authority to identify the particular hospital requirements and specific guidelines which Cephalon was alleged to have breached. This was important not only to ensure that the ruling reflected the facts of the case, but also help Cephalon to implement appropriate corrective and remedial action.

Moreover, Cephalon requested guidance from the Authority on how to address compliance with Clause 17.8 in circumstances where the individual hospital requirements were unclear and unspecific, such as in this case in relation to the provision of free stock. Cephalon submitted that the Code did not provide guidance on how a company should ensure compliance with hospital policy. In these circumstances, Cephalon submitted that it was not unreasonable for the company representative to approach a senior staff member of the hospital who ought to be able to advise or direct the company representative, where appropriate, to the relevant personnel to provide guidance on the local drug

policy requirements for, and expectation on provision of medicines.

Cephalon accepted that although there had been a technical breach of the Misuse of Drugs regulations, this could not be properly characterised as serious given the facts of this case. Cephalon respectfully requested that the Appeal Board consider the facts and amend the language used to characterise the breach accordingly.

As regards the ruling of a breach of Clause 2, as explained above Cephalon submitted that it had acted responsively and responsibly; it immediately retrieved the delivered stock as soon as it knew about the complaint subject to the company's internal investigation. Distribution of Cephalon's branded products was governed by distribution and technical agreements requiring its distributor to comply with the applicable laws and regulations during product distribution. Given these facts, the company queried whether the activities described could properly or proportionately be characterised as bringing discredit upon or reducing confidence in the pharmaceutical industry in the context of Clause 2.

Cephalon submitted that its fulfilment of the consultant's order comprised the provision of free stock for the specific purpose of dose titration (consistent with both the terms of the marketing authorization and the SPC) and could not be treated as the provision of samples. Accordingly, Cephalon did not consider that there had been a breach of Clause 17.8. Cephalon requested clarification of the specific hospital guidelines which it had breached.

Cephalon had suspended all activities relating to any requests for titration stock of Effentora made by any physician, pending the final outcome of the case.

COMMENTS FROM THE COMPLAINANT

There were no further comments from the complainant.

APPEAL BOARD RULING

The Appeal Board noted that Cephalon's representative had met the consultant and agreed to supply her with titration stock of Effentora. In an email the representative had stated that 'This will also assist us with moving forward with a formulary application, as to date they have had little experience of Effentora'. It thus appeared that Effentora was not on the hospital formulary. The consultant chaired the local medicines management committee. The free stock of Effentora was supplied such that it by-passed the hospital pharmacy department. The complainant had stated that 'The hospital requirements stated quite clearly that samples and free stock must not be left within the trust'. The Appeal Board noted, however, that the hospital guidelines provided by the complainant included the term 'samples' but not the term 'free stock'. The term 'samples' had not been defined in the hospital guidelines. The Appeal Board had some sympathy with the complainant in that it noted that the hospital guidelines would have been written by hospital staff and in that regard it appeared that their use of the term 'samples' might not be the same as the use in the Code. It was possible that some hospital staff would view the term 'samples' as all embracing. Nonetheless it was not for the Appeal Board to second guess what the hospital guidelines meant. Given that the hospital guidelines did not refer to 'free stock' the supply of Effentora could not have breached those guidelines. The Appeal Board thus ruled no breach of Clause 17.8. The appeal on this point was successful.

The Appeal Board was very concerned about the request form provided by Cephalon headed 'Effentora Titration Stock Request'. The form included a statement 'I can confirm that the above healthcare premises is licensed to receive and store controlled drugs and that the above named person is authorized to take delivery of the Effentora titration stock'. The form required the name of the person authorized to receive the delivery but not their signature; the form did not require the quantity of medicines being requested to be specified. The Appeal Board noted that the requesting consultant's name had been written in block capitals on the form and at the appeal, contrary to Cephalon's previous submission, its representatives agreed that the form had not been signed. The Appeal Board considered that the request form was woefully inadequate for the supply of a Schedule 2 controlled drug. In that regard the Appeal Board was concerned that Cephalon considered this only to be a technical breach of regulation 14(2). As far as the Code was concerned the Appeal Board viewed this as a serious matter.

The Appeal Board noted that a significant quantity (120 tablets) of Effentora had been supplied. The complainant stated that the delivery should have been via the pharmacy department where auditable records of receipt would be maintained. The Appeal Board considered that the delivery of the controlled drugs via the goods receiving department to a nurse in the pain team had the potential to expose individuals to risk or harm. The Appeal Board noted Cephalon's submission that the free stock had been provided in the context of assisting a formulary application ie not for possible use in the hospital consultant's private practice. The Appeal Board noted Cephalon's submission regarding the seniority of the consultant and her position on the local medicines management committee. The Appeal Board considered that in all cases, however, the responsibility under the Code for complying with individual hospital requirements regarding the provision of medicines and samples was with the pharmaceutical company and could not be devolved to the requesting health professional.

The Appeal Board considered that the provision of a Schedule 2 controlled drug without sufficient controls fell short of competent care and brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

During its consideration of the case the Appeal Board noted that the complainant stated that the consultant thought that she had expressed an interest in the product rather than her signature being taken as an order. However the Appeal Board was concerned that a hospital consultant had accepted the offer of a direct supply of a Schedule 2 controlled drug. The consultant had accepted a wholly inadequate order form which she had neither signed nor stated the quantity to be supplied. The Appeal Board decided that the complainant should be advised of these concerns and assurances sought from her that the matter would be thoroughly investigated in a proper way involving the chief executive and head of governance so as to ensure that any future supplies of controlled drugs, for hospital use, would be appropriately supplied. If such assurances were not forthcoming from the complainant then the Chairman and Director would contact the hospital's chief executive and head of governance directly.

Complaint received **25 January 2010**

Case completed **8 June 2010**

CASE AUTH/2298/2/10

JOHNSON & JOHNSON/DIRECTOR v GLAXOSMITHKLINE CONSUMER HEALTHCARE

NiQuitin 21mg Clear Patch mailing

Johnson & Johnson complained about a mailing sent by GlaxoSmithKline Consumer Healthcare to promote NiQuitin 21mg Clear Patch (nicotine replacement therapy NRT)). The leaflet and a covering letter each bore the same reference and the date of preparation for both was December 2009. NiQuitin Clear was indicated for the relief of nicotine withdrawal symptoms including cravings as an aid to smoking cessation.

As possible breaches of the undertakings given in Cases AUTH/1253/11/01 and AUTH/1401/12/02 were alleged, that part of the case was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The detailed responses from GlaxoSmithKline Consumer Healthcare are given below.

The six page, gate folded leaflet was entitled 'Which therapeutic nicotine patch delivers more nicotine faster than any other patch?' A diagonal flash on the front page referred to 'New data'.

Page 2 of the leaflet was headed 'From day one' followed by the claim 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch' which was referenced to Fant *et al* (2000) and data on file. Beneath, a graph showed comparative mean adjusted plasma nicotine concentrations from a single dose of NiQuitin 21mg patch or Nicorette 25mg patch over 32 hours. Data for the graph came from the data on file.

Johnson & Johnson alleged that the claim was ambiguous and misleading primarily due to lack of clarity relating to the measures of speed and extent of nicotine delivery upon which the claim was based. The reference to 'more' nicotine being delivered 'faster' with NiQuitin than with other patches could relate to higher and more rapid peak plasma level C_{max}, higher and more rapid total nicotine delivery (area under the curve (AUC)) or higher nicotine levels at every timepoint measured.

The data presented appeared to show that the C_{max} was higher and achieved more rapidly with the NiQuitin patch. However, it was not clear from the page whether the difference was statistically significant. Irrespective of the statistical significance, C_{max} was of little clinical relevance for nicotine patches which were designed to deliver sustained, steady plasma levels over an extended period. It might be that the data presented indicated that C_{max} was achieved more rapidly with the NiQuitin 21mg patch, but this was not the same as delivering 'more nicotine faster…'. C_{max} was not a measure of the amount of nicotine delivered but a snap shot of plasma levels at a one time point.

As the Nicorette 16 hour patch was intended to be removed after 16 hours it delivered its nicotine dose faster than the NiQuitin 21mg patch which was intended to be removed after 24 hours. Indeed, the NiQuitin patch would continue to deliver nicotine for eight hours after the Nicorette patch had been removed. The 'full therapeutic dose' of nicotine was thus delivered considerably quicker with the Nicorette patch than with the NiQuitin patch.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare had noted that NiQuitin Clear 21mg patch could be worn for 16 or 24 hours. Johnson & Johnson submitted that this might be true but the NiQuitin patch was clearly intended to be used for 24 hours. The summary of product characteristics (SPC) stated: 'NiQuitin Clear patches should be applied once a day … preferably soon after waking, and worn continuously for 24 hours … . Patches may be removed before going to bed if desired. However, use for 24 hours is recommended to optimise the effects against morning cravings'. Johnson & Johnson submitted that the vast majority of clinical evidence for the NiQuitin patch was from clinical studies of 24 hour usage.

As regards the AUC, this was a measure of the total amount of nicotine delivered. Therefore, Johnson & Johnson believed that this measure was of particular relevance to the claim at issue. In the context of a patch applied daily, the claim 'delivers more nicotine faster' could only reasonably be assumed to refer to the total delivery of nicotine as measured by AUC. Given that AUCs for the two patches would always be measured or calculated over a specific period (eg $AUC_{0\text{-}24}$), for the comparison to be fair this time should be the same for both patches. One patch could not deliver its measured AUC faster than another patch. Comparative AUCs could be higher but not faster.

Another possible interpretation of the claim was that NiQuitin 21mg Clear patch delivered a higher level of nicotine at each time point. This was not the case as levels were higher for the Nicorette 25mg patch at 12 and 14 hours.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare justified 'faster' and 'more' independently of each other. Even if these two individual statements were true, this did not mean

that the overall claim which linked the amount of nicotine delivered and speed of delivery could be justified. Johnson & Johnson objected to the use of the claim which linked the attributes of speed and quality ie 'more nicotine faster.'; it was unclear as to what this 'more' nicotine, which was apparently being delivered faster, equated to.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare had stated that a pharmacokinetic study demonstrated that time to C_{max} (T_{max}) was significantly less for NiQuitin 21mg (6 hours) than Nicorette 25mg patch (12 hours), (p<0.0001). Data were also cited for C_{max}, which according to GlaxoSmithKline Consumer Healthcare, was 18.34ng/ml for NiQuitin and 16.56ng/ml for Nicorette (p=0.0021). However, Johnson & Johnson had been unable to verify these values as the data on file summary provided indicated that the C_{max} for NiQuitin Clear 21mg was 16.5ng/ml measured at 8 hours and 15.7ng/ml measured at 12 hours for the Nicorette 25mg patch.

Regardless of the actual data, C_{max} was a snapshot of the overall plasma profile and could not be used to justify a general claim that 'more nicotine' was delivered 'faster' than any other patch.

As regards the 'more' aspect of the claim, GlaxoSmithKline Consumer Healthcare argued that the $AUC_{0\text{-infinity}}$ for NiQuitin was higher than for Nicorette 25mg patch (382.4ng/ml*hr vs 243.7ng/ml*hr; p<0.0001). Johnson & Johnson did not disagree that the data presented appeared to support that the AUC was higher for NiQuitin but this did not mean that the amount delivered, as measured by the AUC, was delivered faster. The fact that T_{max} appeared to occur earlier with NiQuitin Clear 21mg compared with Nicorette 25mg patch could not justify that the total amount of nicotine delivered was delivered faster.

The Panel considered that the headline claim at issue would be read in conjunction with the prominent graph beneath. The graph compared the mean adjusted plasma nicotine concentrations of single dose NiQuitin 21mg patch with single dose Nicorette 25mg patch over 32 hours; the total area under the curve was greater for the NiQuitin patch which also reached its C_{max} (T_{max}) more rapidly (6 hours vs 12 hours; p<0.0001).

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that speed of delivery and AUC were related. Fant *el al* to which the claim was referenced was a pharmacokinetic crossover study to compare the absorption characteristics of three transdermal nicotine patches; a 15mg 16 hour patch, a 21mg 24 hour patch and NiQuitin 21mg 24 hour patch. The authors stated that the study demonstrated significant differences in nicotine delivery among transdermal patches at the highest marketed dose and approved duration of use. GlaxoSmithKline Consumer Healthcare did not refer to Fant *et al* in its response. Mention was made of Geiss *et al* dated 2010. The data on file to which both the claim at issue and graph were referenced was an open label study the primary objective of which was to demonstrate that NiQuitin 21mg patch was superior to Nicorette 25mg patch with respect to the $AUC_{0\text{-infinity}}$. One of the secondary objectives was to compare the products' single dose C_{max} and T_{max}. The study showed that, compared with the Nicorette 25mg patch, the NiQuitin 21mg patch had a statistically significantly higher $AUC_{0\text{-infinity}}$ (p<0.0001) and earlier T_{max} (6 hours vs 12 hours; p<0.0001). The NiQuitin 21mg patch also had a higher C_{max} (18.34ng/ml vs 16.56ng/ml).

Given the data set out above, the Panel did not consider that the claim 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch', in conjunction with the graph below, was ambiguous or misleading in relation to either C_{max} or AUC as alleged. Nor did the Panel consider that the claim in conjunction with the graph misleadingly implied higher nicotine levels for NiQuitin 21mg patch at each time point measured. The graph clearly showed that NiQuitin 21mg patch had higher nicotine concentrations at all time points other than at 12 and 14 hours when Nicorette 25mg patch had higher nicotine concentrations. The Panel considered that the claim was not misleading as alleged and thus ruled no breach of the Code.

Page 4 of the mailing (the centre inside page) headed 'Continuous daily use' featured a graph comparing plasma nicotine concentration (ng/ml) over time for NiQuitin 21mg patch, Nicorette 15mg patch and Nicotinell 21mg patch. The NiQuitin 21mg patch achieved higher peak plasma nicotine levels than either of the other two patches. The data shown was referenced to Fant *et al*.

Johnson & Johnson was concerned that the presentation of the data implied clinical superiority in terms of smoking cessation outcomes for the NiQuitin patch over other NRT patches, in particular the Nicorette 25mg patch.

Upon opening the leaflet the reader was presented with three consecutive pages comparing the NiQuitin 21mg patch with other NRT patches. The first page [considered above] displayed the single dose pharmacokinetic profiles for NiQuitin 21mg patch and Nicorette 25mg patch. The second of the three pages [ie the page now in question] presented a graph (adapted from Fant *et al*) showing the multiple dose pharmacokinetic profiles for three NRT patches. The third page included comparative efficacy claims relating to smoking cessation and compared NiQuitin 21mg patch with other NRT patches and Nicorette 25mg patch specifically.

Johnson & Johnson considered that the clear overall message of this three page spread was that the NiQuitin 21mg patch had a 'superior' single and multiple dose pharmacokinetic profile compared with other NRT patches and was therefore superior in terms of clinical efficacy. There was no evidence

to support this. Indeed, the 2008 Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

Johnson & Johnson noted that in Case AUTH/1253/11/01 the claim, 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette Patch', was alleged to be misleading as it linked pharmacokinetics to clinical efficacy. The claim was followed by a graph which was derived from Fant *et al*, used to support claims made in the current mailing. In its ruling, the Panel noted that the claim at issue was followed by a comparative efficacy discussion and in its opinion implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more smokers being able to successfully quit than with Nicorette. This was not known to be so and a breach of the Code was ruled.

Johnson & Johnson noted that in inter-company dialogue GlaxoSmithKline Consumer Healthcare did not deny that the mailing was presented in a way that could mislead the reader into believing that differences in pharmacokinetic profiles related to differences in smoking cessation outcomes. On the contrary, GlaxoSmithKline Consumer Healthcare had argued that based on the results of Tonnesen *et al* (1999), it had been established empirically and agreed conceptually that a product's pharmacokinetic profile was relevant to both symptom relief and cessation efficacy, and that it had been shown in a direct clinical comparison that NiQuitin 21mg patch achieved a significantly higher C_{max} and $AUC_{0\text{-}infinity}$, and a faster T_{max} than Nicorette 25mg.

Tonnesen *et al* was a double-blind, randomised, multicentre trial in 3,575 smokers to determine whether higher dosage and longer duration nicotine patch therapy increased success rates. The study demonstrated that 15mg and 25mg patches were superior to placebo and that the 25mg patch was superior to the 15mg patch. Tonnesen *et al* did not assess the efficacy of patches of any other strength, nor provide any comparative data with 24 hour patches. Furthermore, the study did not examine the pharmacokinetic profiles of the patches tested, nor whether these related in any way to efficacy.

In the absence of direct comparative clinical data, it could not be assumed that a higher level of nicotine delivery from a 24 hour patch compared with a 16 hour patch would result in improved efficacy. However, this was precisely what GlaxoSmithKline Consumer Healthcare seemed to suggest. It was possible that factors other than the actual amount of nicotine delivered could result in differences in clinical outcome eg it was yet to be established whether the break from nocturnal nicotine provided by the 16 hour patch was clinically beneficial.

Regardless of the above, there was no evidence to suggest that the different pharmacokinetic profiles observed with the 24 hour patch would result in improved clinical outcomes compared with any strength of 16 hour patch. Johnson & Johnson did not argue that pharmacokinetic profiles were not clinically relevant but simply that differences in pharmacokinetic profiles had not been proven to be of importance in terms of smoking cessation outcomes. Highlighting differences in pharmacokinetic profiles between patches, in the context of claims relating to the comparative efficacy, implied proven differences in terms of smoking cessation. This had not been proven to be the case.

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that its response on this point covered both the leaflet and covering letter. The Panel noted that whilst the leaflet might be read in light of the comments in the covering letter each had to be able to stand alone as regards the requirements of the Code. The Panel noted that Johnson & Johnson's allegations concerned the leaflet and were considered accordingly. The Panel noted that, nonetheless, some of its rulings might be relevant to the covering letter.

The Panel noted that when the leaflet was fully open three consecutive pages compared NiQuitin 21mg patch with other NRT patches. The left hand page featured the single dose pharmacokinetic data described above. The central page, headed 'Continuous daily use' featured a prominent graph comparing the plasma nicotine concentrations measured over 3 days' use of NiQuitin 21mg patch, Nicorette 15mg patch or Nicotinell 21mg patch. The claim 'By building on the previous 24 hours of delivery, NiQuitin 21mg Clear Patch delivers 30% higher blood levels of nicotine once steady state is reached, compared to day one' appeared above the graph. A claim beneath 'Smoking lapses are more likely to occur on the days morning cravings are elevated' was referenced to Shiffman *et al* (1997); it was then stated that 'NiQuitin 21mg 24-hour patch provides more effective protection against morning cravings and cravings throughout the day, than Nicorette 15mg 16-hour patch' referenced to Shiffman and Ferguson (2008). The next page was headed 'Proven short- and long-term quit rates' which compared the quit rate and efficacy of NiQuitin 21mg Patch with other NRT patches. With regard to quit rates this section claimed that no other patch had been shown to be more effective at 4 and 52 weeks including the Nicorette 25mg Invisipatch.

The Panel did not accept GlaxoSmithKline Consumer Healthcare's submission that the leaflet had three distinct sections none of which was a sub section to another. The design of the leaflet was such that the eye was naturally drawn from left to right across the three pages; from the pharmacokinetic data to the clinical claims regarding short- and long-term quit rates.

The Panel noted that Johnson & Johnson's complaint was that the leaflet presented pharmacokinetic data in such a way as to imply superiority in terms of smoking cessation outcomes for the NiQuitin 21mg patch over other NRT patches in particular the Nicorette 25mg patch. The complaint was not about differences in cigarette cravings or nicotine withdrawal symptoms.

The Panel noted that the three page spread of the leaflet presented, from left to right, single dose pharmacokinetic data (discussed above), multiple dose pharmacokinetic data (both of which implied advantages for NiQuitin 21mg patch) and then a page headed 'Proven short- and long-term quit rates'. In the Panel's view it was not unreasonable that readers might assume that the proven short- and long-term quit rates were as a direct consequence of the apparently favourable pharmacokinetic profiles depicted on the previous two pages. Given that the pharmacokinetic data implied advantages for the NiQuitin 21mg patch then it might be expected that the product produced better quit rates which was not so. Claims on the third page of the three-page spread noted and highlighted the percentage of short and long-term quitters on NiQuitin 21mg patch (~60% and ~20% respectively). In the Panel's view the use of highlighted figures implied an advantage for NiQuitin 21mg patch whereas it was possible that all NRT patches might result in quit rates of ~60% and ~20% at 4 and 52 weeks respectively. Indeed, under each of the claims it was stated that no other patch had been found to be more effective. In that regard the Panel noted that the Cochrane Review of 2008 had found no evidence of a difference in effect between 16 hour and 24 hour patches.

The Panel considered that whilst pharmacokinetic data was useful such data must not be presented in a way that implied consequential clinical benefits unless a direct link between the two had been established. The Panel considered that the leaflet was misleading as alleged on this point; it implied that the differences in pharmacokinetic profiles led to differences in quit rates and this had not been proven. A breach of the Code was ruled.

The Panel noted Johnson & Johnson's reference to Case AUTH/1253/11/01 and the claim 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette patch', referenced to Fant *et al*. In Case AUTH/1253/11/01 the Panel had noted that Fant *et al* was a pharmacokinetic study not an efficacy study. The claim at issue in that case followed a comparative efficacy discussion and, in the Panel's view, implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more smokers being able to successfully quit than with Nicorette. This was not known. The claim was considered misleading in this regard.

Turning to the present case the Panel noted that although there were some differences between Case AUTH/1253/11/01 and the leaflet presently at issue, both presented pharmacokinetic data from Fant *et al* including a graph depicting comparative nicotine concentrations. The Panel noted its ruling above of a breach in the present case as it had been implied that the differences in pharmacokinetic profiles resulted in differences in quit rates. In that regard the Panel thus considered that the leaflet in question was in breach of the undertaking given in Case AUTH/1253/11/01. A breach of the Code was ruled. High standards had not been maintained. A breach was ruled. Failure to comply with the undertaking in this instance brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The third page of the three-page inside spread was headed 'Proven short- and long-term quit rates' and featured two claims in highlighted boxes. The first claim read '~60% of abrupt quitters remain quit at 4 weeks with NiQuitin 21mg Clear Patch' referenced to the Transdermal Nicotine Study Group (TNSG) (1991) and Shiffman *et al* (2002).

Johnson & Johnson noted that the TNSG publication reported the results from two multicentre, clinical trials using 21, 14 or 7mg patches over 24 hours. The two studies were randomised, double-blind, placebo-controlled, parallel group trials of 6 weeks' duration and included 935 patients. Successful abstainers were then entered into a third trial for weaning (6 weeks) and off-drug follow up (12 weeks). Short-term abstinence rates for the two trials were measured as smoking cessation during the last 4 weeks of the 6 week full dose period. Abstinence at 6 weeks was 61%, 48%, and 27% for the 21mg, 14mg and placebo patches respectively. The main outcome measure repeatedly referred to in the paper was 4 weeks of continuous abstinence measured at 6 weeks, not smoking cessation measured at 4 weeks.

Shiffman *et al* (2002) reported data from two studies. The first was the TNSG study referred to above and the second was a study comparing nicotine lozenge with placebo. As already stated, the main outcome measure for the TNSG study was abstinence at 6 weeks.

GlaxoSmithKline Consumer Healthcare confirmed that the outcome measure for the TNSG study was 4 weeks' continuous abstinence measured at 6 weeks. Johnson & Johnson thus alleged that the claim that '~60% of abrupt quitters remain quit at 4 weeks with NiQuitin 21mg Clear Patch' was inaccurate and misleading.

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that readers would be familiar with 4 week quit rates as they were a routine NHS measurement and referred to 4 week quit rates, carbon monoxide (CO) verified continuous abstinence measured at 6 weeks. The Panel noted that the abstinence rates in the TNSG study were CO verified; 61% of subjects were continuously abstinent at the end of 6 weeks;

p≤0.001 vs placebo. The Panel noted that the claim at issue read '~60 of abrupt quitters *remain* quit at 4 weeks …' (emphasis added). The Panel considered that it was thus sufficiently clear that the claim referred to continuous abstinence. The Panel did not consider it misleading to not state that the 4 week data was measured at the 6 week time point. Readers would be familiar with how 4 week quit data was measured. The Panel did not consider that the claim was misleading as alleged; no breach of the Code was ruled.

The claim 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch' appeared beneath the claim at issue above within the same highlighted box. Johnson & Johnson stated that the claim at issue was a top parity claim which it understood meant under the Code that there were direct comparative data and hence the NiQuitin 21mg patch had been shown to be at least as effective as other available patches in head-to-head comparisons. This was not so.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare believed that the Code did not require the claim to be supported with direct head-to-head comparisons. However in Case AUTH/1402/12/02, GlaxoSmithKline Consumer Healthcare complained about a very similar claim for Nicorette Patch ie 'No other patch is proven more effective at beating cigarettes' and alleged that '…top parity claims could not be made without head-to-head comparisons with all other patches, which had not been done'. The Panel ruled that the claim implied Nicorette Patch was the most effective patch at beating cigarettes and ruled a breach of the Code. Johnson & Johnson therefore alleged that the claim now at issue was in breach of the Code.

The Panel noted that whilst top parity claims were not prohibited under the Code care should be taken to ensure that they did not give a misleading impression of a product's relative efficacy, were capable of substantiation and otherwise complied with the Code. Every case had to be considered on its own merits. The context in which a claim appeared was important.

The Panel noted that both parties referred to Case AUTH/1402/12/02 wherein the claims 'No other patch offers smokers a greater chance of success', 'No other patch is proven more effective at beating cigarettes' and 'No other nicotine patch works harder at beating cigarettes …' were ruled in breach. The Panel had noted that there was no comparative data on all the available nicotine patches. The claims implied that Nicorette patch was the most effective patch at beating cigarettes. No material or comment in relation to substantiation of the claims was provided. On the data before it the Panel considered that the claims were not capable of substantiation.

Turning back to the case now before it, Case AUTH/2298/2/10, the Panel noted GlaxoSmithKline Consumer Healthcare's submission that there was no evidence to suggest that other nicotine patches were any more effective than NiQuitin patches as assessed by 4 week quit rates. The Panel, however, noted the company's subsequent submission that it was not aware of any data on 4 week quit rates for Nicotinell 21mg patches. In that regard the Panel considered the claim 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch' was misleading. Further, context was important. The Panel considered that the comparative theme of the leaflet meant that the claim at issue was likely to be read as a superiority claim and was thus misleading in this regard. Breaches of the Code were ruled.

The second highlighted box on the third page of the centre of the leavepiece featured the claim: '~ 20% of quitters remain quit at 52 weeks with NiQuitin 21mg Clear Patch' referenced to Aubin *et al* (2008). Johnson & Johnson noted that it was not stated that Aubin *et al* was an open-label study which was a critical piece of information that the reader should know. In Case AUTH/2203/1/09, the Panel stated regarding this study; '… 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 inter-company dialogue GlaxoSmithKline Consumer Healthcare argued that Aubin *et al* was presented as one example, not the data set in its entirety which was why the open-label design did not need to be stated. Johnson & Johnson disagreed. No other supporting reference was given and the reader had not been provided with all the necessary information to assess the claim based on the single reference provided.

The Panel noted each party's submission about Aubin *et al* and Case AUTH/2203/1/09 wherein Aubin *et al* was the sole data set to support a superiority claim for varenicline vs NRT. The Panel considered that the present case was different. Aubin *et al* was being used for its NRT results and there was other data including Richmond *et al*, a randomised, placebo-controlled trial, to the support claim at issue. The Panel considered that the claim '~20% of quitters remain quit at 52 weeks with NiQuitin 21mg Clear Patch' was not misleading as alleged. No breach of the Code was ruled.

The claim 'No other patch has been shown to be more effective at 52 weeks, including Nicorette 25mg Invisipatch' appeared beneath the claim considered above within the same highlighted box. For the same reasons described above, Johnson & Johnson alleged that the claim implied superiority for the NiQuitin 21mg patch over other patches. As already stated, there were no head-to-head studies showing that the NiQuitin 21mg patch was more effective than marketed patches. For the reasons outlined above breaches of the Code were alleged.

The Panel noted that the Cochrane Review 2008 stated 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'. The Panel considered its comments above about context and the comparative theme of the leaflet were nonetheless relevant. The Panel considered that given the comparative nature of the leaflet the claim was likely to be read as a superiority claim and was thus misleading in this regard. Breaches of the Code were ruled.

The covering letter was headed 'Which therapeutic nicotine patch delivers more nicotine faster than any other patch?' and began by discussing the pharmacokinetic data at issue above. Subsequent paragraphs discussed morning cravings and general effectiveness.

Johnson & Johnson referred to the claim 'Reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch' which appeared as the first of two bullet points near the start of the letter. Although the graph within the leaflet appeared to support this claim, as discussed above, Johnson & Johnson had been unable to verify the values given by GlaxoSmithKline Consumer Healthcare for the comparative C_{max} values and it had not been made clear whether these differences were statistically significant. Irrespective of statistical significance, C_{max} was of minimal clinical relevance for nicotine patches which were designed to deliver steady levels of nicotine over a prolonged period of time. Inclusion of this claim, particularly in such a prominent position in the letter, implied that this data was relevant to the clinical scenario and the decision to prescribe NiQuitin 21mg patch rather than Nicorette 25mg Invisipatch.

In inter-company dialogue, GlaxoSmithKline Consumer Healthcare stated that it believed that the delivery characteristics of the patch were fundamental to its clinical success. However, as already stated, Johnson & Johnson was not aware of any data to suggest that the NiQuitin 21mg patch was superior in terms of clinical success compared with Nicorette 25mg patch. There were no data whatsoever to suggest that time to peak plasma concentration was relevant to the choice of which patch to prescribe. Peak plasma level was given undue prominence in the letter suggesting that it was clinically important. This was not so. Johnson & Johnson thus believed that the claim was misleading.

The Panel considered its comments above about the pharmacokinetic data and clinical outcome were relevant; the consequential link between the pharmacokinetic data and the clinical claims had not been established. A reader would not unreasonably assume that the favourable pharmacokinetic data led to the favourable clinical data discussed subsequently in the letter; effective relief from morning cravings and effectiveness at 4 and 52 weeks. The causal link had not been established and the claim was misleading in this regard. A breach of the Code was ruled.

The letter contained the following paragraph: '16-hour patch wear means that blood nicotine concentrations drop to minimal levels overnight when the patch is removed and may be why NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15mg 16-hour patches. Even though most lapses happen later in the day, they are more likely to occur on the days when morning cravings are elevated'.

Johnson & Johnson believed that the suggestion that nocturnal nicotine dosing with the 24-hour patch '…may be why NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15 mg 16-hour patches' was speculation. Johnson & Johnson was not aware of any robust data demonstrating that wearing a patch overnight was related to improved cravings scores throughout the day. There could be a number of reasons to explain differences between the 21mg 24 hour patch and 15mg 16 hour patch in cravings relief including difference in overall strength between the two.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare cited the NiQuitin 21mg patch SPC which stated: 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'. This statement related to morning cravings. It did not support the claim at issue which suggested that nocturnal nicotine dosing might provide more effective protection against cravings throughout the day.

The Panel noted GlaxoSmithKline Consumer Healthcare's submissions that the claim at issue was written as postulation, and did not state that 24-hour patch wear was the only possible explanation, and that Johnson & Johnson had not provided any data to refute the suggestion that nocturnal dosing might be related to an improvement in cravings throughout the day. The Panel noted that claims had to be capable of substantiation.

The Panel noted that the NiQuitin 21mg patch SPC stated that use for 24 hours was recommended to optimise effect against morning cravings. The claim at issue related to 'protection against cravings throughout the day'. The Panel noted that the only data showing improved craving control throughout the day for the 24-hour patch was for heavily dependent smokers rather than the general smoking population (Shiffman *et al* 2000). The Panel considered that the phrase 'may be' was insufficient to negate the impression that nocturnal nicotine dosing did provide more effective protection against cravings throughout the day in the general smoking population. This impression was compounded by the subsequent paragraph which referred to optimizing protection against morning cravings (in

line with the SPC) and providing a level of nicotine in the blood stream on waking that could be built on with the application of the next patch. A subsequent claim referred to NiQuitin 21mg patch's general effectiveness compared to other patches. The Panel considered the claim at issue misleading as alleged. A breach of the Code was ruled.

Johnson & Johnson was concerned that the paragraph referred to above represented breaches of the Code including a breach of a previous undertaking. The first claim '… NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15mg 16-hour patches' was referenced to Shiffman *et al* (1997) (reference 3). The second claim 'Even though most lapses happen later in the day, they are more likely to occur on the days when morning cravings are elevated' was referenced to Shiffman and Ferguson (2008) (reference 4).

Shiffman *et al* (1997) was a non-comparative study which assessed urge and lapse in smokers who had recently quit. It did not demonstrate that the NiQuitin 21mg patch provided more effective protection against cravings than the Nicorette patch. GlaxoSmithKline Consumer Healthcare had acknowledged that the referencing was wrong and agreed to correct this in future iterations. Johnson & Johnson assumed that references 3 and 4 had been mixed up.

Shiffman and Ferguson was an analysis of two randomised clinical studies. The first study cited compared a 21mg 24 hour patch with a placebo patch (n=102) while the second study compared a 21mg 24 hour patch with a 15mg 16 hour patch (n=244). Overall the authors concluded that the first study showed that the 21mg patch was effective in reducing cravings throughout the day compared with placebo and that the second study showed that cravings were lower at all times during the day with the 21mg patch compared with the 15mg patch.

Johnson & Johnson noted that in Case AUTH/1401/12/02 the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' was ruled in breach of the Code. It was alleged that the claim contributed to the overall impression that 24 hour patches had greater efficacy in achieving smoking cessation than 16 hour patches. There were no data available at the time to show clinical differences between 16 and 24 hour patches and this situation had not changed. Indeed, the 2008 Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

In the letter now at issue, Johnson & Johnson believed that the reader would assume that the stated reduction in cravings throughout the day apparently achieved with 24-hour patches was such that NiQuitin 21mg patch had greater efficacy in achieving smoking cessation compared with the 16 hour patch. This was compounded by the link to lapses in the proceeding claim.

Moreover, Shiffman *et al* (1997), which Johnson & Johnson believed was the reference GlaxoSmithKline Consumer Healthcare intended to use to support the claim that morning cravings and lapses were linked (this was the case for the accompanying leaflet), was conducted in smokers who had recently quit and were not using pharmacotherapy to treat their nicotine withdrawal. There was no evidence to suggest that the pattern of cravings and lapses was the same as for the patients being treated with NRT. Therefore, for all the reasons cited, Johnson & Johnson believed that these claims were in breach. It also believed that the implication that improvements in cravings relief were associated with higher smoking cessation outcomes was a breach of undertaking.

The Panel noted Johnson & Johnson's allegation that there was no evidence to suggest that the pattern of cravings and lapses in Shiffman *et al* (1997) applied to patients being treated with NRT. The Panel did not accept that Figure 1 in Shiffman and Ferguson provided *prima facie* support as suggested by GlaxoSmithKline Consumer Healthcare; it depicted placebo-controlled data. The study authors noted that smoking lapses commonly occurred in the evening and late night hours but the authors did not observe higher craving during these time periods. The authors noted that many studies had shown that smoking lapses were associated with acute increases in craving when smokers experienced provocative situations and thus the occurrence of such lapses during the evening and night hours might be due to exposure to such stimuli rather than to any inherent diurnal rhythm in the intensity of background craving. The Panel considered the claim was misleading as alleged. A breach of the Code was ruled.

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

The Panel noted that in Case AUTH/1401/12/02 it was alleged that the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' inferred a greater likelihood of success in smoking cessation with a 24-hour patch than with a 16-hour patch. The Appeal Board, *inter alia*, considered that the claim implied that because NiQuitin CQ was effective in relieving morning cravings, it would also be effective in long-term smoking cessation. The phrase 'from the word go' appeared to differentiate NiQuitin CQ from the 16-hour patches referred to in

the preceding paragraph. The Appeal Board considered that the claim implied that NiQuitin CQ 24-hour patch was more likely to help a patient to stop smoking than a 16-hour patch. The Appeal Board considered that the claim overstated the data and was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Turning to the present case, Case AUTH/2298/2/10, the Panel noted that there were some differences between the paragraph at issue and the claim considered previously. Nonetheless, the Panel considered that the claims at issue implied that as lapses were more likely to occur when morning cravings were elevated, the more effective protection against cravings afforded by the 24-hour patch meant that NiQuitin 21mg patch was more likely to help a patient stop smoking than a 16-hour patch. There was no evidence this was so. This impression was misleading, a breach of Clause 7.2 was ruled. Further this impression was contrary to the undertaking given in Case AUTH/1401/12/02 and thus a breach of the Code was ruled. High standards had not been maintained. A breach was ruled. Failure to comply with the undertaking in this instance bought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Johnson & Johnson noted that the claim 'No other patch is proven more effective than NiQuitin 21mg Clear Patch at 4 or 52 weeks' in the letter was very similar to the claims about short- and long-term quit rates in the leaflet. Johnson & Johnson alleged, as described above, that the claim implied superiority in terms of cessation rates for the NiQuitin 21mg patch over other patches. This was not so and thus Johnson & Johnson believed that this claim was in breach of the Code.

The Panel considered that rulings above were relevant here. Breaches of the Code were ruled.

Johnson & Johnson Limited complained about the promotion of NiQuitin 21mg Clear Patch (nicotine replacement therapy (NRT)) by GlaxoSmithKline Consumer Healthcare. The material at issue was a mailing which comprised a leaflet and a covering letter, each bore the reference NCQ/SYN/KG/1109/01. The date of preparation for both items was December 2009. Inter-company dialogue had failed to resolve all of the issues. NiQuitin Clear was indicated for the relief of nicotine withdrawal symptoms including cravings as an aid to smoking cessation.

As possible breaches of the undertakings given in Cases AUTH/1253/11/01 and AUTH/1401/12/02 were alleged, that part of the case was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings. The Authority thus asked GlaxoSmithKline Consumer Healthcare to comment in relation to Clauses 2 and 9.1 of the Code as well as Clause 25 referred to by Johnson & Johnson.

A Leaflet

The six page, gate folded leaflet was entitled 'Which therapeutic nicotine patch delivers more nicotine faster than any other patch?' A diagonal flash on the front page referred to 'New data'.

1 Claim 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch'

Page 2 of the leaflet was headed 'From day one' followed by the remainder of the claim at issue which was referenced to Fant *et al* (2000) and data on file. Beneath, a graph showed comparative mean adjusted plasma nicotine concentrations from a single dose of NiQuitin 21mg patch or Nicorette 25mg patch over 32 hours. Data for the graph came from the data on file.

COMPLAINT

Johnson & Johnson alleged that the claim was ambiguous and as such misleading, in breach of Clause 7.2. The ambiguity was primarily due to lack of clarity relating to the measures of speed and extent of nicotine delivery upon which the claim was based. The reference to 'more' nicotine being delivered 'faster' with NiQuitin than with other patches could relate to a number of measures:

- Higher and more rapid peak plasma level (C_{max})
- Higher and more rapid total nicotine delivery (area under the curve (AUC))
- Higher nicotine levels at every timepoint measured.

The data presented appeared to show that the (C_{max}) was higher and achieved more rapidly with the NiQuitin patch. However, it was not clear from the page whether the difference was statistically significant. Irrespective of the statistical significance, C_{max} was of little clinical relevance for nicotine patches which were designed to deliver sustained, steady plasma levels over an extended period. It might be that the data presented indicated that C_{max} was achieved more rapidly with the NiQuitin 21mg patch, but this was not the same as delivering 'more nicotine faster…'. C_{max} was not a measure of the amount of nicotine delivered but merely a snap shot of plasma levels at one time point.

The Nicorette 16 hour patch was intended to be removed after 16 hours and so it delivered its nicotine dose faster than the NiQuitin 21mg patch which was intended to be removed 24 hours after application. Indeed, the NiQuitin patch would continue to deliver nicotine for eight hours after the Nicorette patch had been removed. The 'full therapeutic dose' of nicotine was therefore delivered considerably quicker with the Nicorette patch than with the NiQuitin patch.

In inter-company dialogue GlaxoSmithKline

Consumer Healthcare had noted that NiQuitin Clear 21mg patch could be worn for 16 or 24 hours. Johnson & Johnson submitted that this might be true but the NiQuitin patch was clearly intended to be used for 24 hours; the summary of product characteristics (SPC) stated: 'NiQuitin Clear patches should be applied once a day, at the same time each day and preferably soon after waking, to a non-hairy, clean, dry skin site and worn continuously for 24 hours. The NiQuitin Clear patch should be applied promptly on removal from its protective sachet. Patches may be removed before going to bed if desired. However, use for 24 hours is recommended to optimise the effects against morning cravings'.

The vast majority of clinical evidence for the NiQuitin patch was from clinical studies of 24 hour usage.

As regards the AUC, this was a measure of the total amount of nicotine delivered. Therefore, Johnson & Johnson believed that this measure was of particular relevance in the context of the claim that 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch'.

In the context of a patch applied daily, the claim 'delivers more nicotine faster' could only reasonably be assumed to refer to the total delivery of nicotine as measured by AUC. Given that AUCs for the two patches would always be measured or calculated over a specific period (eg $AUC_{0\text{-}24}$) and that for the comparison to be fair, this time should be the same for both patches. One patch clearly could not deliver its measured AUC faster than another patch. Comparative AUCs could be higher but not faster.

Another possible interpretation of the claim was that NiQuitin 21mg Clear patch delivered a higher level of nicotine at each time point. This was not the case as levels were higher for the Nicorette 25mg patch at 12 and 14 hours.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare justified 'faster' and 'more' independently of each other. Even if these two individual statements were true, this did not mean that the overall claim which linked the amount of nicotine delivered and speed of delivery could be justified. Johnson & Johnson objected to the use of the claim which linked the attributes of speed and quality ie 'more nicotine faster.'; it was unclear as to what this 'more' nicotine, which was apparently being delivered faster, equated to.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare had stated that a pharmacokinetic study demonstrated that time to C_{max} (T_{max}) was significantly less for NiQuitin 21mg (6 hours) than Nicorette 25mg patch (12 hours) ($p<0.0001$). Data were also cited for C_{max}, which according to GlaxoSmithKline Consumer Healthcare, was 18.34ng/ml for NiQuitin and 16.56ng/ml for Nicorette ($p=0.0021$). However, Johnson & Johnson had been unable to verify these values as the data on file summary provided indicated that the C_{max} for NiQuitin Clear 21mg was 16.5ng/ml measured at 8 hours and 15.7ng/ml measured at 12 hours for the Nicorette 25mg patch.

Regardless of the actual data, C_{max} was simply a snapshot of the overall plasma profile and could not be used to justify a general claim that 'more nicotine' was delivered 'faster' than any other patch.

As regards the 'more' aspect of the claim, GlaxoSmithKline Consumer Healthcare argued that the $AUC_{0\text{-}infinity}$ for NiQuitin was higher than for Nicorette 25mg patch (382.4ng/ml*hr vs 243.7ng/ml*hr; $p<0.0001$). Johnson & Johnson did not disagree that the data presented appeared to support that the AUC was higher for NiQuitin but this did not mean that the amount delivered, as measured by the AUC, was delivered faster. The fact that T_{max} appeared to occur earlier with NiQuitin Clear 21mg compared with Nicorette 25mg patch could not justify that the total amount of nicotine delivered was delivered faster.

Johnson & Johnson alleged that the claim was ambiguous and misleading in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson initially believed that the ambiguity of the claim at issue was primarily due to lack of clarity relating to the measures of speed and extent of nicotine delivery upon which the claim was based. The company then listed three possible interpretations;

- Higher and more rapid C_{max}

The data supported this interpretation. C_{max} was significantly higher with the NiQuitin 21mg patch ($p=0.0031$) and time to reach the peak concentration was significantly faster with the NiQuitin 21mg patch ($p<0.0001$) (Geiss *et al* 2010).

- Higher and more rapid total nicotine delivery.

The data on file supported this interpretation. The primary endpoint of the study was $AUC_{0\text{-}infinity}$ and this was shown to be statistically significantly higher with NiQuitin 21mg patch ($p<0.0001$).

- Higher nicotine levels at every time point measured.

The claim did not state 'delivers more nicotine at each time point'; it stated that the NiQuitin 21mg patch delivered more nicotine faster. The clear and simple graphics were unambiguous and displayed the time points where NiQuitin 21mg patch levels were numerically lower than the comparator with clear white space between the lines, ensuring that even a casual reader would not believe that NiQuitin 21mg patch had higher nicotine levels at each individual time point.

It was clear from the slope of the graphs from the head-to-head studies in the leaflet that NiQuitin 21mg patch delivered nicotine more rapidly than other patches. It was also clear (and Johnson & Johnson agreed), that it delivered more nicotine to the patient than the Nicorette 25mg patch as the $AUC_{0\text{-infinity}}$ was higher ($p<0.0001$). The initial rapid rise in nicotine levels were then maintained and contributed to a higher AUC. The shape of the graphs themselves determined the area underneath them, and therefore the amount of nicotine that the individual was exposed to in a given time. Thus the two features of speed of delivery and AUC were related.

GlaxoSmithKline Consumer Healthcare submitted that Johnson & Johnson had confused the issue by asserting that because Nicorette was only worn for 16 hours, it delivered its 'full therapeutic dose' faster. This was not relevant because Nicorette 16 hour patches continued to deliver about 20% of their dose after removal of the patch due to absorption of nicotine from the skin depot (Benowitz *et al* 1992, Johansson *et al* 1996). Thus although only worn for 16 hours, part of the 'full therapeutic dose' continued to be delivered after its removal. Also the SPC for NiQuitin 21mg patch made it clear that it was also able to be used as a 16 hour patch if desired. There were no caveats in the SPC regarding 16 or 24 hour wear apart from the desire to do so. However, the SPC highlighted that 24 hour wear optimised the effect against morning cravings as it was important for prescribers and users to understand the risks and benefits of 24 hour and 16 hour wear and this was recognised by the licensing authority. C_{max}, $AUC_{0\text{-}16}$, and $AUC_{0\text{-infinity}}$ assuming a 16 hour application of the 21mg patch were also significantly higher, (Geiss *et al*) so the claim in question still held true whether NiQuitin 21mg patch was worn for 16 or 24 hours.

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson further stated that in the context of a patch applied daily, the claim 'delivers more nicotine faster' could only reasonably be assumed to refer to the total delivery of nicotine as measured by AUC and that for the comparison to be fair, this time should be the same for both patches. GlaxoSmithKline Consumer Healthcare agreed with this interpretation and was confused as Johnson & Johnson appeared to contradict its initial assertion that the claim was ambiguous. GlaxoSmithKline Consumer Healthcare agreed that AUC had to be assessed over the same time period for both patches and it was. Although duration of patch wear was different between the patches, the calculations were based on the same time period over all. The primary end point was $AUC_{0\text{-infinity}}$ and this was statistically significantly higher for NiQuitin 21mg ($p<0.0001$). It was also significantly higher in a post hoc analysis of $AUC_{0\text{-}16}$ and $AUC_{0\text{-infinity}}$ assuming a 16 hour application of the 21mg patch (Geiss *et al*).

NiQuitin's AUC was bigger than Nicorette's AUC over the same time period. If more nicotine was delivered per unit time then this was the definition of rate and thus faster. No claims were made for specific C_{max} levels in any materials, but simply that NiQuitin 21mg patch 'reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch', which was supported by the comparative T_{max} data (6 vs 12 hours; $p<0.0001$) (Geiss *et al*). GlaxoSmithKline Consumer Healthcare explained that the apparent discrepancy in the values in the data on file table and the actual C_{max} values calculated in the study was because the nicotine concentrations cited in the data on file table were the mean nicotine levels at each time point whereas the C_{max} in the study synopsis was the mean of each individual's C_{max}.

The claim was substantiated by the data which Johnson & Johnson agreed showed that NiQuitin 21mg patch delivered more nicotine (greater AUC) faster (more rapid rise of nicotine levels, earlier T_{max}). Delivery of drug per unit time was the rate of delivery. NiQuitin 21mg patch delivered more nicotine per unit time, thus supporting the claim that it delivered more nicotine faster. The data showed it also had a higher C_{max} than Nicorette 25mg although no claims were made in this regard.

Thus GlaxoSmithKline Consumer Healthcare refuted the allegation that the claim was ambiguous and misleading, in breach of Clause 7.2.

PANEL RULING

The Panel considered that the headline claim at issue would be read in conjunction with the prominent graph beneath. The graph compared the mean adjusted plasma nicotine concentrations of single dose NiQuitin 21mg patch with single dose Nicorette 25mg patch over 32 hours; the total area under the curve was greater for the NiQuitin patch which also reached its C_{max} (T_{max}) more rapidly (6 hours vs 12 hours; $p<0.0001$).

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that speed of delivery and AUC were related. Fant *el al* to which the claim at issue was referenced was a pharmacokinetic crossover study to compare the absorption characteristics of three transdermal nicotine patches; a 15mg 16 hour patch, a 21mg 24 hour patch and NiQuitin 21mg 24 hour patch. The authors stated that the study demonstrated significant differences in nicotine delivery among transdermal patches at the highest marketed dose and approved duration of use. GlaxoSmithKline Consumer Healthcare did not refer to Fant *et al* in its response. Mention was made of Geiss *et al* dated 2010. The data on file to which both the claim at issue and graph were referenced was an open label study the primary objective of which was to demonstrate that NiQuitin 21mg patch was superior to Nicorette 25mg patch with respect to the $AUC_{0\text{-infinity}}$. One of the secondary objectives was to compare the products' single dose C_{max} and T_{max}. The study showed that, compared with the Nicorette 25mg patch, the NiQuitin 21mg patch had a statistically significantly higher $AUC_{0\text{-infinity}}$

($p<0.0001$) and earlier T_{max} (6 hours vs 12 hours; $p<0.0001$). The NiQuitin 21mg patch also had a higher C_{max} (18.34ng/ml vs 16.56ng/ml).

Given the data set out above, the Panel did not consider that the claim 'From day one NiQuitin 21mg Clear Patch delivers more nicotine faster than any other therapeutic nicotine patch', in conjunction with the graph below, was ambiguous or misleading in relation to either C_{max} or AUC as alleged. Nor did the Panel consider that the claim at issue in conjunction with the graph misleadingly implied higher nicotine levels for NiQuitin 21mg patch at each time point measured. The accompanying graph clearly showed that NiQuitin 21mg patch had higher nicotine concentrations at all time points other than at 12 and 14 hours when Nicorette 25mg patch had higher nicotine concentrations. The Panel considered that the claim was not misleading as alleged and thus ruled no breach of Clause 7.2.

2 Implied improvements in efficacy based on pharmacokinetic data

Page 4 of the mailing (the centre inside page) headed 'Continuous daily use' featured a graph comparing plasma nicotine concentration (ng/ml) over time for NiQuitin 21mg patch, Nicorette 15mg patch and Nicotinell 21mg patch. The NiQuitin 21mg patch achieved higher peak plasma nicotine levels than either of the other two patches. The data shown was referenced to Fant *et al*.

COMPLAINT

Johnson & Johnson was concerned that the presentation of the data implied clinical superiority in terms of smoking cessation outcomes for the NiQuitin patch over other NRT patches, in particular the Nicorette 25mg patch.

Upon opening the leaflet the reader was presented with three consecutive pages comparing the NiQuitin 21mg patch with other NRT patches. The first page [considered in Point A1 above] displayed the single dose pharmacokinetic profiles for NiQuitin 21mg patch and Nicorette 25mg patch. The second of the three pages [ie the page now in question] presented a graph (adapted from Fant *et al*) showing the multiple dose pharmacokinetic profiles for three NRT patches. The third page included comparative efficacy claims relating to smoking cessation and compared NiQuitin 21mg patch with other NRT patches and Nicorette 25mg patch specifically.

Johnson & Johnson considered that the clear overall message of this three page spread was that the NiQuitin 21mg patch had a 'superior' single and multiple dose pharmacokinetic profile compared with other NRT patches and was therefore superior in terms of clinical efficacy. There was no evidence to support this. Indeed, the 2008 Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

Johnson & Johnson believed that there were parallels to be drawn with Case AUTH/1253/11/01 in which it was alleged that the claim 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette Patch' was misleading as it linked pharmacokinetics to clinical efficacy. The claim was followed by a graph which was derived from Fant *et al*, used to support claims made in the current mailing. In its ruling, the Panel noted that the claim at issue was followed by a comparative efficacy discussion and in its opinion implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more smokers being able to successfully quit than with Nicorette. This was not known to be so and a breach of the Code was ruled.

Johnson & Johnson noted that in inter-company dialogue GlaxoSmithKline Consumer Healthcare did not deny that the mailing was presented in a way that could mislead the reader into believing that differences in pharmacokinetic profiles related to differences in smoking cessation outcomes. On the contrary, GlaxoSmithKline Consumer Healthcare had argued that based on the results of Tonnesen *et al* (1999), it had been established empirically and agreed conceptually that a product's pharmacokinetic profile was relevant to both symptom relief and cessation efficacy, and that it had been shown in a direct clinical comparison that NiQuitin 21mg patch achieved a significantly higher C_{max} and $AUC_{0\text{-infinity}}$, and a faster T_{max} than Nicorette 25mg.

Tonnesen *et al* was a double-blind, randomised, multicentre trial in 3,575 smokers to determine whether higher dosage and longer duration nicotine patch therapy increased success rates. The study compared 15mg and 25mg 16 hour patches with placebo and demonstrated that both patches were superior to placebo and that the 25mg patch was superior to the 15mg patch. Tonnesen *et al* did not assess the efficacy of patches of any other strength, nor provide any comparative data with 24 hour patches. Furthermore, the study did not provide any information relating to the pharmacokinetic profiles of the patches tested, nor whether these related in any way to efficacy.

In the absence of direct comparative clinical data, it could not be assumed that a higher level of nicotine delivery from a 24 hour patch compared with a 16 hour patch would result in improved efficacy. However, this was precisely what GlaxoSmithKline Consumer Healthcare seemed to suggest. It was possible that factors other than the actual amount of nicotine delivered could result in differences in clinical outcome. For instance it was yet to be established whether the break from nocturnal nicotine provided by the 16 hour patch could result in a clinical benefit.

Regardless of the above, there was no evidence to suggest that the different pharmacokinetic profiles observed with the 24 hour patch would result in improved clinical outcomes compared with any strength of 16 hour patch. Johnson & Johnson did not argue that pharmacokinetic profiles were not clinically relevant as suggested by GlaxoSmithKline Consumer Healthcare, but simply that differences in pharmacokinetic profiles had not been proven to be of importance in terms of smoking cessation outcomes for nicotine patches.

Highlighting differences in pharmacokinetic profiles between patches, in the context of claims relating to the comparative efficacy, implied proven differences in terms of smoking cessation. This had not been proven to be the case. Therefore, Johnson & Johnson alleged a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson had alleged that the comparative pharmacokinetic data depicted graphically implied clinical superiority with regard to smoking cessation outcomes; it believed there were parallels to be drawn from Case AUTH/1253/11/01.

The undertaking given by GlaxoSmithKline Consumer Healthcare in relation to the ruling of a breach of Clause 7.2 in Case AUTH/1253/11/01 was to more clearly link the clinical relevance of comparative pharmacokinetic profiles to relief of craving rather than directly following discussion of long-term successful quitting compared with placebo. The leaflet and letter now at issue were sufficiently different so that they did not breach this previous undertaking. The leaflet and the letter were provided as one item and as such GlaxoSmithKline Consumer Healthcare had considered them together as similar allegations were made by Johnson & Johnson in relation to the letter.

The letter discussed the new pharmacokinetic data for NiQuitin 21mg/24hr compared with Nicorette 25mg/16hr patches, followed by a comparison of craving relief (not quit rates) between NiQuitin 21mg/24hr and Nicorette 15mg/16hr in a separate paragraph. This was then followed by the relief of morning cravings by 24 hour wear of NiQuitin 21mg/24hr patch, and that was followed by a sentence on quit rates that specifically did not state that rates were higher with NiQuitin 21mg Clear patch. The headline and highlighted take out message from the letter was that NiQuitin 21mg Clear patch delivered more nicotine than other patches, not that it had higher quit rates. The reader was then referred to the enclosed leaflet for further information on the new data, below which was the headline claim for that study.

The leaflet had three distinct sections, the first of which discussed the new pharmacokinetic data for NiQuitin 21mg/24hr compared with Nicorette 25mg/16hr patches, the second compared pharmacokinetic profiles for three NRT patches and compared craving relief (not quit rates) between NiQuitin 21mg/24hr and Nicorette 15mg/16hr patches, the third discussed short- and long-term quit rates. None of the three sections was a sub section to another.

Johnson & Johnson alleged that the overall message of the three page spread was that the NiQuitin 21mg patch had a superior pharmacokinetic profile and therefore had superior clinical efficacy. Johnson & Johnson stated that it did not argue that pharmacokinetic profiles were not clinically relevant…but simply that differences in pharmacokinetic profiles had not been proven to be of importance in terms of smoking cessation outcomes for nicotine patches. Throughout its complaint Johnson & Johnson consistently assumed that smoking cessation was the only point of clinical relevance for health professionals and therefore any data provided would be interpreted in the context of long-term quit rates. Also, its interpretation of 'clinical efficacy' related solely to smoking cessation. In addition to that quoted above, GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson quoted the following from the 2008 Cochrane Review, 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch:..'. Johnson & Johnson had also stated that there was no evidence to suggest that the different pharmacokinetic profiles observed with the 24 hour patch would result in improved clinical outcomes compared with any strength of 16 hour patch. The same assumptions and interpretation were also evident in Johnson & Johnson's comments regarding GlaxoSmithKline Consumer Healthcare's discussion of Tonnesen *et al*, the quotations from which had been picked and presented in such a way that their meaning had been altered (further comment on Tonnesen *et al* was made below).

Clinical efficacy is not just quit rates

GlaxoSmithKline Consumer Healthcare noted that NiQuitin 21mg patches were indicated for 'the relief of nicotine withdrawal symptoms including cravings as an aid to smoking cessation'. Thus 'clinical efficacy' referred not just to smoking cessation but also craving relief. It was therefore appropriate to discuss both in promotional materials. Efficacy in the reduction of cravings and withdrawal symptoms had long been recognised as an important clinical endpoint as evidenced by the licensed indications of both oral and transdermal NRT products. Furthermore in the eight years since the rulings made in Case AUTH/1253/11/01, there had been a clear shift in views regarding the role of NRT with more emphasis on the importance of the clinical benefits of relief of craving and withdrawal symptoms, to the point that NRT indications were not restricted solely to quit rates, although abstinence was the preferred goal. In 2006 the Regulatory Authority authorised a temporary abstinence indication and in 2009 had approved a 'harm reduction' indication on one of Johnson & Johnson's nicotine products.

Cochrane only relevant for long-term quit rates not symptom relief

Regarding the quotations above from Johnson & Johnson's complaint, Cochrane (Stead *et al* 2009) explicitly focused on long-term (at least 6 months) cessation rates as the outcome of interest; in the context of craving relief therefore Cochrane was irrelevant.

In the only head-to-head study of NiQuitin 21mg patch and Nicorette 15mg 16hr patch, it was not only craving and symptom control that was greater with the NiQuitin 21mg patch, but also abstinence, although no claims were made in this regard (Shiffman *et al* 2000). This study was not included in the Cochrane review as it did not report long-term quit rates, only short-term ones. However it was useful to demonstrate the possible link between differing pharmacokinetic and clinical outcomes in terms of craving control and symptom relief. Thus it was irrelevant to quote Cochrane 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch…' to make the argument that there was no evidence to support superior clinical efficacy as craving control and symptom relief were not within the remit of the Cochrane review but were valid clinical outcomes. GlaxoSmithKline Consumer Healthcare's materials accurately represented the level of evidence available and did not claim or imply superior long-term quit rates.

With regard to the ruling of a breach of Clause 7.2 in Case AUTH/1253/11/01, GlaxoSmithKline Consumer Healthcare understood of that ruling that discussion of pharmacokinetics, craving relief and quit rates in the same item was not prohibited, but that these discussions must be presented in such a way that pharmacokinetic profiles were not taken to imply a difference in long-term quit rates between patches. Each item must be considered on its own merits and GlaxoSmithKline Consumer Healthcare considered the leaflet in question sufficiently different such that it did not breach any previous undertaking.

In both the letter and the leaflet the discussion on pharmacokinetics and craving relief was clearly separate from the discussion of quit rates and there were no claims that one impacted the other. The flow and separation of the information were in line with GlaxoSmithKline Consumer Healthcare's previous undertakings and did not imply that the pharmacokinetic differences were of clinical significance in terms of long-term quit rates compared with other patches.

Thus GlaxoSmithKline Consumer Healthcare refuted Johnson & Johnson's allegation of implied clinical superiority in relation to long-term quit rates and a breach of Clause 7.2. GlaxoSmithKline Consumer Healthcare also refuted the implied breach of Clause 25.

Additional comments

Johnson & Johnson noted that in inter-company dialogue, GlaxoSmithKline Consumer Healthcare did not deny that the mailing was presented in such a way that could mislead the reader into believing that differences in pharmacokinetic profile related to differences in smoking cessation outcomes. While GlaxoSmithKline Consumer Healthcare did not explicitly deny this allegation, it was implicit in its response that it refuted it. This point could have easily been further clarified by inter-company dialogue.

Johnson & Johnson went on to cite a statement by GlaxoSmithKline Consumer Healthcare about Tonnesen *et al* and asserted that it used the trial to justify the alleged link between pharmacokinetic data and cessation rates. Johnson & Johnson had used the quotation out of context and as such had misrepresented GlaxoSmithKline Consumer Healthcare's position. Tonnesen *et al*, one of the largest randomised clinical trials of NRT, conducted by Johnson & Johnson's predecessor company, Pharmacia, was discussed in response to the implication that reporting of pharmacokinetic data was not of relevance or value to health professionals.

In making the general case for the relevance of pharmacokinetic data to health professionals GlaxoSmithKline Consumer Healthcare discussed the findings of Tonnesen *et al* which included a dose-response effect for long-term efficacy and suppression of tobacco withdrawal symptoms. Contrary to Johnson & Johnson's statement that 'Tonnesen *et al* did not provide any information relating to the pharmacokinetic profiles of the patches tested', the paper reported 'Plasma nicotine concentrations for the four nicotine patch arms for successful subjects (point prevalence) who used the patch every day'. Tonnesen *et al* compared 15mg/16hr with 25mg/16hr (achieved by 15mg/16hr + 10mg/16hr) nicotine transdermal patches and found a dose response effect. The most logical explanation for this was the pharmacokinetic profile. Thus the general case was made for the relevance of pharmacokinetic data. However, GlaxoSmithKline Consumer Healthcare continued to acknowledge that direct comparative studies were not available for long-term quit rates between the two nicotine transdermal patches marketed by the respective companies and maintained that no claims had been made in that regard and no previous undertakings had been breached in that respect.

It was, however, important that prescribers knew that there were clinical differences in the craving relief offered by different patches in some populations (Shiffman *et al* 2000) and this would affect patient experience. There was interest in how this difference in craving relief might be achieved and as such, pharmacokinetic data were of interest and relevance to prescribers.

Health professionals had a duty to understand the

products they prescribed and recommended and pharmacokinetic profiles were a fundamental part of that understanding.

PANEL RULING

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that its response on this point covered both the leaflet and covering letter. The Panel noted that whilst the leaflet might be read in light of the comments in the covering letter each had to be capable of standing alone as regards the requirements of the Code. The Panel noted that Johnson & Johnson's allegations concerned the leaflet and were considered accordingly. The Panel noted that, nonetheless, some of its rulings might be relevant to the covering letter.

The Panel noted that when the leaflet was fully open three consecutive pages compared NiQuitin 21mg patch with other NRT patches. The left hand page featured the single dose pharmacokinetic data described at Point A1, above. The central page, headed 'Continuous daily use' featured a prominent graph comparing the plasma nicotine concentrations measured over 3 days' use of NiQuitin 21mg patch, Nicorette 15mg patch or Nicotinell 21mg patch. The claim 'By building on the previous 24 hours of delivery, NiQuitin 21mg Clear Patch delivers 30% higher blood levels of nicotine once steady state is reached, compared to day one' appeared above the graph. A claim beneath 'Smoking lapses are more likely to occur on the days morning cravings are elevated' was referenced to Shiffman *et al* (1997); it was then stated that 'NiQuitin 21mg 24-hour patch provides more effective protection against morning cravings and cravings throughout the day, than Nicorette 15mg 16-hour patch' referenced to Shiffman and Ferguson (2008). The next page was headed 'Proven short- and long-term quit rates' which compared the quit rate and efficacy of NiQuitin 21mg Patch with other NRT patches. With regard to quit rates this section claimed that no other patch had been shown to be more effective at 4 and 52 weeks including the Nicorette 25mg Invisipatch.

The Panel did not accept GlaxoSmithKline Consumer Healthcare's submission that the leaflet had three distinct sections and that none of the three sections was a sub section to another. Each page featured a common colour scheme and design format such that the reader's eye was naturally drawn from left to right across the three pages; from the pharmacokinetic data to the clinical claims regarding short- and long-term quit rates.

The Panel noted that Johnson & Johnson's complaint was that the leaflet presented pharmacokinetic data in such a way as to imply superiority in terms of smoking cessation outcomes for the NiQuitin 21mg patch over other NRT patches in particular the Nicorette 25mg patch. The complaint was not about differences in cigarette cravings or nicotine withdrawal symptoms.

The Panel noted that the three page spread of the leaflet presented, from left to right, single dose pharmacokinetic data (discussed at Point A1 above), multiple dose pharmacokinetic data (both of which implied advantages for NiQuitin 21mg patch in terms of AUC, C_{max} and T_{max}) and then a page headed 'Proven short- and long-term quit rates'. In the Panel's view it was not unreasonable that readers might assume that the proven short- and long-term quit rates were as a direct consequence of the apparently favourable pharmacokinetic profiles depicted on the previous two pages. Given that the pharmacokinetic data implied advantages for the NiQuitin 21mg patch then it might be expected that the product produced better clinical results in terms of quit rates which was not so. Claims on the third page of the three-page spread noted and highlighted the percentage of short-term and long-term quitters on NiQuitin 21mg patch (~60% and ~20% respectively). In the Panel's view the use of highlighted figures implied an advantage for NiQuitin 21mg patch whereas it was possible that all NRT patches might result in quit rates of ~60% and ~20% at 4 and 52 weeks respectively. Indeed, under each of the claims it was stated that no other patch had been found to be more effective. In that regard the Panel noted that the Cochrane Review of 2008 had found no evidence of a difference in effect between 16 hour and 24 hour patches.

The Panel considered that whilst readers might find pharmacokinetic data useful care must be taken not to present such data in a way that implied consequential clinical benefits unless a direct link between the two had been established. The Panel considered that the leaflet was misleading as alleged on this point; it implied that the differences in pharmacokinetic profiles led to differences in quit rates and this had not been proven. A breach of Clause 7.2 was ruled.

The Panel noted that Johnson & Johnson had also referred to Case AUTH/1253/11/01 wherein the claim 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette patch', referenced to Fant *et al* was ruled in breach of Clause 7.2. In Case AUTH/1253/11/01 the Panel had noted that Fant *et al* was a pharmacokinetic study not an efficacy study. The claim at issue in that case followed a comparative efficacy discussion and, in the opinion of the Panel, implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more smokers being able to successfully quit than with Nicorette. This was not known. The claim was considered misleading in this regard.

Turning to the present case the Panel noted that there were some differences between Case AUTH/1253/11/01 and the leaflet presently at issue. However, both presented pharmacokinetic data from Fant *et al* including a graph depicting comparative nicotine concentrations. The Panel noted its ruling above of a breach of the Clause 7.2 in the present case as it had been implied that the differences in

pharmacokinetic profiles resulted in differences in quit rates. In that regard the Panel thus considered that the leaflet in question was in breach of the undertaking given in Case AUTH/1253/11/01. A breach of Clause 25 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. Failure to comply with the undertaking in this instance brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

3 Abstinence at 4 weeks

Page 5 (the third page of the three-page inside spread) was headed 'Proven short- and long-term quit rates' and featured two claims in highlighted boxes. The first claim read '~60% of abrupt quitters remain quit at 4 weeks with NiQuitin 21mg Clear Patch'. This claim was referenced to a publication by the Transdermal Nicotine Study Group (TNSG) (1991) and a poster by Shiffman *et al* (2002), presented at the Society for Research on Nicotine and Tobacco in Spain.

COMPLAINT

Johnson & Johnson noted that the TNSG publication reported the results from two multicentre, controlled clinical trials using 21, 14 or 7mg patches over 24 hours. The two studies were randomised, double-blind, placebo-controlled, parallel group trials of 6 weeks' duration and included 935 patients. Successful abstainers were then entered into a third trial for weaning (6 weeks) and off-drug follow up (12 weeks). Short-term abstinence rates for the two trials were measured as smoking cessation during the last 4 weeks of the 6 week full dose period. Abstinence at 6 weeks was 61%, 48%, and 27% for the 21mg, 14mg and placebo patches respectively. The main outcome measure repeatedly referred to in the paper was 4 weeks of continuous abstinence measured at 6 weeks, not smoking cessation measured at 4 weeks.

Shiffman *et al* (2002) reported data from two studies. The first was the TNSG study referred to above and the second was a study comparing nicotine lozenge with placebo. As already stated, the main outcome measure for the TNSG study was abstinence at 6 weeks.

GlaxoSmithKline Consumer Healthcare confirmed that the outcome measure for the TNSG study was 4 weeks' continuous abstinence measured at 6 weeks. Therefore, Johnson & Johnson alleged that the claim that '~60% of abrupt quitters remain quit at 4 weeks with NiQuitin 21mg Clear Patch' was inaccurate and hence misleading in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that four week quit rates were a routine measure used by NHS Stop Smoking Services and would be familiar to readers. Within the NHS, 4 week quit rates were measured up to six weeks after the quit date (West 2005). Similarly in the TNSG study four week quit rates were carbon monoxide (CO) verified continuous abstinence measured at 6 weeks. This meant that the first couple of weeks of the study did not count towards the measurement of the 4 week quit rate. GlaxoSmithKline Consumer Healthcare used the phrase 'remain quit' to convey the message of continuous abstinence rather than point prevalence which would not have required the participants to have been abstinent for the entire 4 weeks.

Quit rates declined over days and weeks as participants lapsed, so the continuous abstinence quit rates were higher the earlier in the quit attempt that they were measured. Johnson & Johnson did not dispute that 60% were still quit at 6 weeks. Since this was measured by continuous abstinence during the previous 4 weeks, then those ~60% must also have been quit 2 weeks earlier at 4 weeks from baseline. Whichever way it was interpreted it was true that ~60% abrupt quitters remained quit at 4 weeks with NiQuitin 21mg patch.

The target audience for the leaflet was familiar with 4 week quite rates and how they were measured up to 6 weeks.

Thus GlaxoSmithKline Consumer Healthcare denied the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that readers would be familiar with 4 week quit rates as they were a routine NHS measurement and referred to 4 week quit rates, CO verified continuous abstinence measured at 6 weeks. The Panel noted that the abstinence rates in the TNSG study were CO verified; 61% of subjects were continuously abstinent at the end of 6 weeks; $p \leq 0.001$ vs placebo. The Panel noted that the claim at issue read '~60 of abrupt quitters **remain** quit at 4 weeks …' (emphasis added). The Panel considered that it was thus sufficiently clear that the claim referred to continuous abstinence. The Panel did not consider it misleading to not state that the 4 week data was measured at the 6 week time point. Readers would be familiar with how 4 week quit data was measured. The Panel did not consider that the claim was misleading as alleged; no breach of Clause 7.2 was ruled.

4 Claim 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch'

This claim appeared beneath the claim at issue at Point A3 above within the same highlighted box.

COMPLAINT

Johnson & Johnson stated that the claim at issue was a top parity claim which it understood meant under the Code that there were direct comparative data and hence the NiQuitin 21mg patch had been shown to be at least as effective as other available patches in head-to-head comparisons. This was not so.

Johnson & Johnson noted that GlaxoSmithKline Consumer Healthcare believed that the Code did not require the above claim to be supported with direct head-to-head comparisons. However in Case AUTH/1402/12/02, GlaxoSmithKline Consumer Healthcare complained about a very similar claim made for Nicorette Patch ie 'No other patch is proven more effective at beating cigarettes' and had alleged that '…top parity claims could not be made without head-to-head comparisons with all other patches, which had not been done'. The Panel ruled that the claim implied Nicorette Patch was the most effective patch at beating cigarettes and ruled a breach of the Code.

Johnson & Johnson therefore alleged that the claim at issue was in breach of Clauses 7.2 and 7.3.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that the issues raised were the evidence needed to support a top parity claim and whether a top parity claim could be made under the Code without implying superiority. In Case AUTH/1402/12/02 it was the Panel which ruled that the claim 'No other patch is proven more effective at beating cigarettes' implied superiority. However, each case must be considered on its own merits and in the current environment.

GlaxoSmithKline Consumer Healthcare submitted that, by definition, top parity was not the same as superiority. A superiority claim would state that 'x is more effective than y' and GlaxoSmithKline Consumer Healthcare firmly believed that any manufacturer holding appropriate data to support such a claim would word it in that way. As such a top parity claim would not be used if superiority data were available. A superiority claim could be used to clearly communicate the availability of evidence to show that x was more effective than y, whereas a top parity claim could be used to show that there was no evidence to suggest that other products in the category were any more effective than the product in question. A lack of evidence of a product attribute was not the same thing as evidence of a lack of that product attribute. The differences between a superiority claim and a top parity claim were clear, as illustrated by those used in the leaflet:

Superiority: 'NiQuitin 21mg 24-hour patch provides more effective protection against morning cravings and cravings throughout the day than Nicorette 15mg 16-hour patch'*

Top parity: 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch'

The superiority claim clearly communicated the existence of comparative data and specifically cited those data as a reference. The top parity claim clearly communicated that there were no data that had shown otherwise and as such no reference was cited.

- GlaxoSmithKline Consumer Healthcare noted that this wording had been lifted directly from the leaflet to illustrate the difference between superiority and top parity claims. However GlaxoSmithKline Consumer Healthcare recognised that this claim required the inclusion of the population studied in Shiffman *et al* (2000) in order to comply with previous undertakings.

NRT was only made available on NHS prescription in April 2001 and thus NHS staff exposure to and knowledge of this product area was fairly limited when the previous ruling was made compared with today. In the years since that ruling, there had been significant government investment to developing the NHS Stop Smoking Services, expanding the role of various health professionals in this area. Helping smokers to quit had become much wider than 'prescribers' in the traditional sense. As a result of the introduction of patient group directions and primary care trust voucher schemes the following groups might now be involved in smoking cessation: stop smoking advisors, pharmacists, practice nurses, dentists, midwives, GPs and pharmacy and healthcare assistants. These audiences now received many materials on this therapy area, including promotional materials for NRT. Depending on content and purpose, these materials would have been approved under either the ABPI Code or the Proprietary Association of Great Britain (PAGB) codes. All NRT products had a general sales list (GSL) legal classification and as such were promoted to consumers, non-prescribing health professionals and prescribing health professionals under codes which explicitly allowed top parity claims and had established levels of evidence required to support them. As such, this wide range of health professionals saw materials for the same products approved under the ABPI Code and under other codes, depending on whether their intention was to promote the prescription of the medicine or its recommendation/sale. They would therefore have been frequently exposed to top parity claims and superiority claims in this therapeutic area which straddled over the counter (OTC) and prescription sales.

While the ABPI Code differed from others in that it did not specifically permit top parity claims or provide guidance on the level of evidence needed to support them, there was no clause in the Code that prohibited them. Since the wide range of health professionals in this particular therapeutic area already received materials containing top parity

claims, GlaxoSmithKline Consumer Healthcare considered it reasonable to apply consistency with respect to these types of claim to its health professional audiences, as they would not distinguish between which materials had been approved under which codes. In GlaxoSmithKline Consumer Healthcare's view, if consumers and non-prescribers could be considered able to distinguish between top parity and superiority claims, as evidenced by other codes governing promotion of medicines, this would certainly be true of prescribers, who of course were not isolated from communications containing such claims aimed principally at other audiences.

For the reasons presented above, GlaxoSmithKline Consumer Healthcare considered that in the specific arena of NRT, the top parity claim 'No other patch has been shown to be more effective at 4 weeks…' did not breach the Code and did not mislead the audience. It accurately reflected that there was no evidence to suggest that other nicotine patches were any more effective than NiQuitin patches as assessed by 4 week quit rates. This led to the second point raised by Johnson & Johnson, the data required to support a top parity claim.

It seemed logical to take into account any guidance already provided regarding the substantiation of top parity claims in materials directed at health professionals. Under the PAGB Professional Code, top parity claims were considered valid when the evidence indicated that no other relevant product was superior. Head-to-head, comparative data on all products falling within the scope of comparative statements were not required. Head-to-head data were only required in support of a superiority claim. The same was true for the substantiation of top parity claims in materials aimed at consumer audiences.

The ~60% 4 week quit rate had previously been contested by Pfizer under the PAGB Code and found to reflect the available data by the PAGB and so the complaint was not upheld.

Most studies on nicotine patches looked at long-term (six months plus) quit rates and did not always report earlier quit rates. However, Tonnesen *et al* compared Nicorette 15mg patches with Nicorette 15mg +10mg patches and placebo and reported quit rates at week 4. These were 50.6%, 40.9% and 27.7% for 25mg, 15mg and placebo respectively. Overall, at all time points 25mg was significantly better than 15mg patch. It was on the basis of this study that Johnson & Johnson promoted the 25mg Invisipatch as more effective than its 15mg patch and so therefore one needed only compare 4 week quit rates for NiQuitin 21mg patch with 25mg 4 week quit rates as it was established that the 25mg patch was more effective than the 15mg patch.

Although it was difficult to compare across studies, the relative risks for the NiQuitin 21mg patch vs placebo in a large double blind, placebo controlled trial was 2.26 for the 4 week continuous abstinence rate at 6 weeks (61/27 = 2.26) and 2.1 (19/9 = 2.1) for the one year quit rates (TNSG data). In comparison, the relative risks for the 25mg patch vs placebo in Tonnesen *et al* were 1.82 (50.6/27.7 = 1.82) for the 4 week rate and 1.6 (15.9/9.9 = 1.6) for the one year rate. Thus it could be seen that not only numerically 60% vs 51%, but also in comparing relative risks there was no evidence to suggest that other nicotine patches were more effective than NiQuitin 21mg. GlaxoSmithKline Consumer Healthcare was not aware of any data on 4 week quit rates for Nicotinell 21mg patches.

GlaxoSmithKline Consumer Healthcare asserted that this was an appropriate use of a top parity claim for its products that were promoted for prescription and OTC use and it was directed to an audience frequently exposed to top parity claims. Thus GlaxoSmithKline Consumer Healthcare refuted the alleged breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that whilst top parity claims were not prohibited under the Code care should be taken to ensure that they did not give a misleading impression of a product's relative efficacy, were capable of substantiation and otherwise complied with the Code. Every case had to be considered on its own merits. The context in which a claim appeared was important.

The Panel noted that both parties referred to Case AUTH/1402/12/02 wherein the claims 'No other patch offers smokers a greater chance of success', 'No other patch is proven more effective at beating cigarettes' and 'No other nicotine patch works harder at beating cigarettes …' were ruled in breach of Clause 7.4 by the Panel. The Panel had noted that there was no comparative data on all the available nicotine patches. The claims implied that Nicorette patch was the most effective patch at beating cigarettes. No material or comment in relation to substantiation of the claims was provided. On the data before it the Panel considered that the claims were not capable of substantiation.

Turning back to the case now before it, Case AUTH/2298/2/10, the Panel noted GlaxoSmithKline Consumer Healthcare's submission that there was no evidence to suggest that other nicotine patches were any more effective than NiQuitin patches as assessed by 4 week quit rates. The Panel, however, noted the company's subsequent submission that it was not aware of any data on 4 week quit rates for Nicotinell 21mg patches. In that regard the Panel considered the claim 'No other patch has been shown to be more effective at 4 weeks, including Nicorette 25mg Invisipatch' was misleading. Further, context was important. The Panel considered that the comparative theme of the leaflet meant that the claim at issue was likely to be read as a superiority claim and was thus misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

5 Use of Aubin *et al* (2008) to support a 52 week quit claim

The second highlighted box on the third page of the centre of the leavepiece featured the claim: '~ 20% of quitters remain quit at 52 weeks with NiQuitin 21mg Clear Patch' referenced to Aubin *et al* (2008).

COMPLAINT

Johnson & Johnson noted that there was no reference to the fact that Aubin *et al* was an open-label study which was a critical piece of information that the reader should know. In Case AUTH/2203/1/09, the Panel had stated regarding this study:

> '… 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 inter-company dialogue GlaxoSmithKline Consumer Healthcare argued that Aubin *et al* was presented as one example, not the data set in its entirety and that this was why the open-label design did not need to be stated. Johnson & Johnson disagreed. No other supporting reference was given and the reader had not been provided with all the necessary information to assess the claim based on the single reference provided. Johnson & Johnson alleged a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that a one year quit rate of ~20% reflected the data available specific to NiQuitin 21mg patch. It cited Aubin *et al* as one example as the claim itself did not refer to a specific study. It was not the only data available to substantiate the claim, but was an easily accessible, straightforward recent study with which many of the recipients of the leaflet would already be familiar. It appeared in a highly respected, peer reviewed journal, Thorax, and had featured in the NHS prescribing adviser's blog in February 2008 (Robinson 2008) which many of the leaflet's recipients would have read.

Another study of NiQuitin 21mg patch that reported one year quit rates included Richmond *et al* (1997), a randomised, double-blind, placebo-controlled trial in 305 participants. Twelve month quit rates with NiQuitin 21mg patch were around 20% (point prevalence 29%, prolonged abstinence 24% and continuous abstinence 19%).

Another study looked at the additional benefit of NiQuitin 21mg patch on behavioural therapy in 64 participants which achieved one year abstinence rates of 38% in the behavioural therapy plus patch group compared to 22% in those using behavioural therapy alone (Cinciripini *et al* 1996).

Cruse *et al* (2001), an open, observational study following smoking cessation in the workplace using NiQuitin patches and found 20% were non-smokers at the 12 month follow up (15% continuous abstinence plus 5% who had lapsed but had since quit successfully). Case AUTH/2203/1/09 was not relevant here. In that case the claim in question was a superiority claim for Champix vs NRT where Aubin *et al* was the only data available and being used to support the superiority claim in its entirety. In the current case, Aubin *et al* was cited simply as an example of a 20% quit rate but with data from a randomised, double-blind, placebo-controlled trial available to confirm this finding and substantiate the claim further if required.

The claim was supportable by the body of evidence and was not misleading. GlaxoSmithKline Consumer Healthcare refuted the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted each party's submission about Aubin *et al* and Case AUTH/2203/1/09 wherein Aubin *et al* was the sole data set to support a superiority claim for varenicline vs NRT. The Panel considered that the present case was different. Aubin *et al* was being used for its NRT results and there was other data including Richmond *et al*, a randomised, placebo-controlled trial, to the support claim at issue. The Panel considered that the claim '~20% of quitters remain quit at 52 weeks with NiQuitin 21mg Clear Patch' was not misleading as alleged. No breach of Clause 7.2 was ruled.

6 Claim 'No other patch has been shown to be more effective at 52 weeks, including Nicorette 25mg Invisipatch'

This claim appeared beneath the claim considered in Point A5 above, within the same highlighted box.

COMPLAINT

For the same reasons described above at Point A4, Johnson & Johnson alleged that the claim that 'No other patch has been shown to be more effective at 52 weeks…' implied superiority for the NiQuitin 21mg patch over other patches. As already stated, there were no head-to-head studies showing that the NiQuitin 21mg patch was more effective than marketed patches. For the reasons outlined above breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that the same principles applied as discussed in Point A4 and Johnson & Johnson again supplied no evidence to refute the claim as it stood, but believed a top parity claim would be

misunderstood by the readers to mean that NiQuitin 21mg patch was superior to other patches in terms of long-term quit rates. For the reasons previously stated, GlaxoSmithKline Consumer Healthcare asserted that this was an appropriate use of a top parity claim for GSL products that were promoted for prescription and OTC use and it was directed to an audience which was frequently exposed to top parity claims.

The Cochrane Review 2008, as cited by Johnson & Johnson, selected only randomised trials where NRT was compared with placebo or no treatment, or where different doses of NRT were compared. Trials which did not report cessation rates and those with a follow-up of less than 6 months were excluded. The results of the review stated 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

Thus while direct comparative data were not available to prove equivalence or superiority, a large-scale meta-analysis of indirect comparative data showed no evidence to suggest any other patch was more effective than NiQuitin 21mg patch as assessed by long-term quit rates. Hence a superiority claim could not be made but the top parity claim was valid. Thus GlaxoSmithKline Consumer Healthcare refuted alleged breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the Cochrane Review 2008 stated 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'. The Panel considered its comments at Point A4 above about context and the comparative theme of the leaflet were nonetheless relevant. The Panel considered that given the comparative nature of the leaflet the claim was likely to be read as a superiority claim and was thus misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

B Covering letter

The covering letter was headed 'Which therapeutic nicotine patch delivers more nicotine faster than any other patch?' and began by discussing the pharmacokinetic data at issue in Point A1 above. Subsequent paragraphs discussed morning cravings and general effectiveness.

1 Claim 'Reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch'

This claim appeared as the first of two bullet points near the start of the letter.

COMPLAINT

Although the graph within the leaflet appeared to support this claim, as discussed above, Johnson & Johnson had been unable to verify the values given by GlaxoSmithKline Consumer Healthcare for the comparative C_{max} values and it had not been made clear whether these differences were statistically significant. Irrespective of statistical significance, C_{max} was of minimal clinical relevance for nicotine patches. As stated above nicotine patches were designed to deliver steady levels of nicotine over a prolonged period of time. Inclusion of this claim, particularly in such a prominent position in the letter, implied that this data was relevant to the clinical scenario and that the prescriber should take this into account when deciding to prescribe NiQuitin 21mg patch rather than Nicorette 25mg Invisipatch.

In inter-company dialogue, GlaxoSmithKline Consumer Healthcare stated that it believed that the delivery characteristics of the patch were fundamental to its clinical success. However, as already stated, Johnson & Johnson was not aware of any data to suggest that the NiQuitin 21mg patch was superior in terms of clinical success compared with Nicorette 25mg patch.

There were no data whatsoever to suggest that time to peak plasma concentration was of any relevance to the choice of which patch to prescribe. The parameter of peak plasma level was given undue prominence in the letter suggesting that it was clinically important. This was not the case. Therefore, Johnson & Johnson believed that this claim was misleading and a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson had asserted that it was unclear whether C_{max} values for NiQuitin 21mg vs Nicorette 25mg were statistically significant despite this being confirmed in inter-company dialogue. However GlaxoSmithKline Consumer Healthcare considered this was a specious argument as no claims was made about C_{max} itself. As mentioned above, the claim was that NiQuitin 21mg patch 'Reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch' and this was unambiguously supported by the substantial difference in the time to reach peak concentrations between the two patches (6 hours vs 12 hours; $p<0.0001$) (Geiss *et al* 2010).

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson further stated that peak plasma level was given undue prominence in the letter suggesting it was clinically important. The first half of the allegation was untrue. The claim 'Reaches peak nicotine concentrations faster than Nicorette 25mg Invisipatch' appeared only once in the letter and peak plasma levels were not discussed further. Neither did the letter discuss the actual peak plasma concentrations reached. This was hardly undue prominence.

The second half of Johnson & Johnson's sentence asserted that the claim was not clinically relevant. GlaxoSmithKline Consumer Healthcare firmly considered that the pharmacokinetic profile of nicotine delivery systems was of fundamental clinical relevance, as discussed at length in inter-company dialogue. There was no definitive therapeutic level defined for nicotine, whereby one could reliably predict efficacy either in terms of craving, symptom control or abstinence. The threshold for efficacy might vary across individual smokers and at various times during the quitting process. However, it was recognised that there was a dose-response curve for transdermal nicotine patches (as illustrated and discussed in Tonnesen *et al* comparing 15mg and 25mg dosing, and the TNSG trial comparing 21mg, 14mg and 7mg patches). As such, to reach an effective level more quickly (whatever that level was) meant less time at sub-optimal levels and aided morning symptom relief even during the first few days of a quit attempt (Shiffman *et al* 2000), the most difficult days for quitters (Garvey *et al* 1992). Health professionals had a duty to be informed about the products they recommended or prescribed and pharmacokinetics were reported for all relevant products in the licensed details for this very reason. C_{max} and T_{max} were both explicitly discussed even in the Nicorette Invisipatch SPC indicating their relevance and importance to health professionals.

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson also stated that it was not aware of any data to suggest that the NiQuitin 21mg patch was superior in terms of clinical success compared with Nicorette 25mg patch'. No superiority claims were made in this regard. GlaxoSmithKline Consumer Healthcare referred to Point A2 above for further discussion on the relevance of discussing pharmacokinetic data with health professionals.

Thus GlaxoSmithKline Consumer Healthcare refuted the alleged breach of Clause 7.2.

PANEL RULING

The Panel considered its comments at Point A2 about the pharmacokinetic data and clinical outcome were relevant here. The consequential link between the pharmacokinetic data and the clinical claims had not been established. A reader would not unreasonably assume that the favourable pharmacokinetic data led to the favourable clinical data discussed subsequently in the letter; effective relief from morning cravings and effectiveness at 4 and 52 weeks. The causal link had not been established and the claim was misleading in this regard. A breach of Clause 7.2 was ruled.

2 The effect of nocturnal nicotine dosing on cravings

The letter contained the following paragraph:

'16-hour patch wear means that blood nicotine concentrations drop to minimal levels overnight when the patch is removed and may be why NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15mg 16-hour patches. Even though most lapses happen later in the day, they are more likely to occur on the days when morning cravings are elevated'.

COMPLAINT

Johnson & Johnson believed that the suggestion that nocturnal nicotine dosing with the 24-hour patch '…may be why NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15 mg 16-hour patches' was speculation. Johnson & Johnson was not aware of any robust data demonstrating that wearing a patch overnight was related to improved cravings scores throughout the day. There could be a number of reasons to explain differences between the 21mg 24 hour patch and 15mg 16 hour patch in cravings relief including difference in overall strength between the two.

In inter-company dialogue GlaxoSmithKline Consumer Healthcare cited the NiQuitin 21mg patch SPC which stated: 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'. This statement related to morning cravings. It did not support the claim at issue which suggested that nocturnal nicotine dosing might provide more effective protection against cravings throughout the day. Therefore, Johnson & Johnson alleged a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson asserted that the claim was 'pure speculation', however, it had not provided any evidence to refute the suggestion that nocturnal nicotine dosing might be related to an improvement in cravings throughout the day. The letter was written in such a way that it offered a possible explanation for the improved craving control seen with 24 hour patch wear. Improved craving control compared to a 16 hour patch was seen not only in mornings but also throughout the day in heavily dependent smokers (smokers who smoked within 30 minutes of waking and had their worst cravings in the morning) as reported in Shiffman *et al* (2000).

The claim at issue was written as postulation (using the phrase 'may be why') and did not categorically state that this was the only possible explanation.

The regulatory authorities had agreed that 24-hour wear of NiQuitin patches (all strengths ie 21mg, 14mg and 7mg) optimised the effect against morning cravings as stated in the SPCs. They therefore agreed that it was not simply the strength

of the patch that affected craving control, but the duration of application. This finding was relevant and robust enough to form part of the licensed particulars so it was baffling that Johnson & Johnson appeared to dismiss it.

GlaxoSmithKline Consumer Healthcare refuted the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted GlaxoSmithKline Consumer Healthcare's submission that the claim at issue was written as postulation and did not state that 24-hour patch wear was the only possible explanation. The Panel further noted GlaxoSmithKline Consumer Healthcare's submission that Johnson & Johnson had not provided any data to refute the suggestion that nocturnal dosing might be related to an improvement in cravings throughout the day. The Panel noted that claims had to be capable of substantiation.

The Panel noted that the NiQuitin 21mg patch SPC stated that use for 24 hours was recommended to optimise effect against morning cravings. The claim at issue related to 'protection against cravings throughout the day'.

The Panel noted that the only data showing improved craving control throughout the day for the 24-hour patch was for heavily dependent smokers rather than the general smoking population (Shiffman *et al* 2000). The Panel considered that the phrase 'may be' was insufficient to negate the impression that nocturnal nicotine dosing did provide more effective protection against cravings throughout the day in the general smoking population. This impression was compounded by the subsequent paragraph which referred to optimizing protection against morning cravings (in line with the SPC) and providing a level of nicotine in the blood stream on waking that could be built on with the application of the next patch. A subsequent claim referred to NiQuitin 21mg patch's general effectiveness compared to other patches. The Panel considered the claim at issue misleading as alleged. A breach of Clause 7.2 was ruled.

3 Implied greater smoking cessation efficacy based on cravings data

COMPLAINT

Johnson & Johnson was concerned that the paragraph referred to at Point B2 above represented breaches of the Code including a breach of a previous undertaking.

The first claim '… NiQuitin 21mg 24-hour patches also provide more effective protection against cravings throughout the day than Nicorette 15mg 16-hour patches' was referenced to Shiffman *et al* (1997) (reference 3). The second claim 'Even though most lapses happen later in the day, they are more likely to occur on the days when morning cravings are elevated' was referenced to Shiffman and Ferguson (2008) (reference 4).

Shiffman *et al* (1997) was a non-comparative study which assessed urge and lapse in smokers who had recently quit. It did not demonstrate that the NiQuitin 21mg patch provided more effective protection against cravings than the Nicorette patch. GlaxoSmithKline Consumer Healthcare had acknowledged that the referencing was wrong and agreed to correct this in future iterations. Johnson & Johnson assumed that references 3 and 4 had been mixed up.

Shiffman and Ferguson was an analysis of two randomised clinical studies. The studies and the analyses were sponsored by SmithKline Beecham. The first of the two studies cited compared a 21mg 24 hour patch with a placebo patch (n=102) while the second study compared a 21mg 24 hour patch with a 15mg 16 hour patch (n=244). Overall the authors concluded that the first study showed that the 21mg patch was effective in reducing cravings throughout the day compared with placebo and that the second study showed that cravings were lower at all times during the day with the 21mg patch compared with the 15mg patch.

Johnson & Johnson noted that in Case AUTH/1401/12/02, the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' was ruled in breach of Clause 7.3 by the Panel and upheld on appeal. It was alleged that the claim contributed to the overall impression that 24 hour patches had greater efficacy in achieving smoking cessation than 16 hour patches. There were no data available at the time to show clinical differences between 16 and 24 hour patches and this situation had not changed. Indeed, the 2008 Cochrane Review on Nicotine Replacement Therapy for Smoking Cessation stated that 'Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups'.

In the letter now at issue, Johnson & Johnson believed that the reader would assume that the stated reduction in cravings throughout the day apparently achieved with 24-hour patches was such that NiQuitin 21mg patch had greater efficacy in achieving smoking cessation compared with the 16 hour patch. This was compounded by the link to lapses in the proceeding claim.

Moreover, Shiffman *et al* (1997), which Johnson & Johnson believed was the reference GlaxoSmithKline Consumer Healthcare intended to use to support the claim that morning cravings and lapses were linked (this was the case for the accompanying leaflet), was conducted in smokers who had recently quit and were not using

pharmacotherapy to treat their nicotine withdrawal. There was no evidence to suggest that the pattern of cravings and lapses was the same as for the patients being treated with NRT.

Therefore, for all the reasons cited, Johnson & Johnson believed that these claims were in breach of Clause 7.2. It also believed that the implication that improvements in cravings relief were associated with higher smoking cessation outcomes was a breach of undertaking and therefore a breach of Clause 25.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that as agreed in inter-company dialogue, the referencing was incorrect and it had committed to correcting it. The material in question cited Shiffman *et al* (1997) and Shiffman and Ferguson respectively in support of the above claims. The references, however, were cited in the wrong order.

GlaxoSmithKline Consumer Healthcare noted that in Case AUTH/1401/12/02, a breach of the Code was ruled with regard to the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' and upheld on appeal. The Panel considered that linking morning cravings and relapse to a conclusion to recommend NiQuitin to help them quit 'from the word go' resulted in the reader assuming the stated reduction in morning cravings was such that NiQuitin had greater efficacy in achieving smoking cessation compared with the 16-hour patch. The Appeal Board noted that the claim implied that because NiQuitin was effective in relieving morning cravings, it would also be effective in long-term smoking cessation. It also considered that 'from the word go' appeared to differentiate NiQuitin from 16-hour patches. Taken together, these statements implied that NiQuitin 24-hour patch was more likely to help a patient stop smoking than a 16-hour patch and thus overstated the data.

Similar principles applied to those discussed in Point A2 above. While the material in question discussed pharmacokinetics, cravings and quit rates, it did so in line with previous undertakings and made no claim that implied either the pharmacokinetic profile of the NiQuitin 21mg/24hr patch or the craving relief it provided resulted in superior long-term quit rates compared with other patches.

The letter discussed the new pharmacokinetic data for NiQuitin 21mg/24hr compared with Nicorette 25mg/16hr patches, followed by a comparison of craving relief (not quit rates) between NiQuitin 21mg/24hr and Nicorette 15mg/16hr in a separate paragraph. This was followed by the relief of morning cravings by 24 hour wear of NiQuitin 21mg/24hr patch, and that was followed by a sentence on quit rates that specifically did not state that quit rates were higher with NiQuitin 21mg patch. The headline and highlighted take out message from the letter was that NiQuitin 21mg Clear Patch delivered more nicotine than other patches, not that it had higher quit rates. The reader was then referred to the enclosed leaflet for further information on the new data, below which was the headline claim for that study.

The letter was sufficiently different such that it did not breach a previous undertaking. Thus GlaxoSmithKline Consumer Healthcare refuted an alleged breach of Clause 7.2 and of Clause 25 with respect to the undertaking given in Case AUTH/1401/12/02.

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson also alleged that there was no evidence to suggest that the pattern of cravings and lapses reported in Shiffman *et al* (1997) (for smokers who had recently quit without pharmacotherapy) was the same for patients being treated with NRT and therefore questioned GlaxoSmithKline Consumer Healthcare's assertion that morning cravings and lapses were linked in the context of smokers quitting with NRT. However, Johnson & Johnson had provided no evidence to the contrary. Studies of NRT using a placebo comparator showed the same pattern of craving and lapse in both groups although the magnitude and frequency of craving and lapse was less in the active group. Figure 1 in Shiffman and Ferguson, illustrated this in terms of craving. This provided *prima facie* support that the findings of Shiffman *et al* (1997) were also relevant to those using NRT.

GlaxoSmithKline Consumer Healthcare noted that Johnson & Johnson also stated that while GlaxoSmithKline Consumer Healthcare agreed to amend claims in response to points raised on the leaflet, it failed to acknowledge breaches of the Code for the covering letter. GlaxoSmithKline Consumer Healthcare noted that in its response to Johnson & Johnson it agreed that a breach of undertaking relating to Case AUTH/1253/11/01 had occurred with respect to the requirement to include the details of the subgroup studied in Shiffman *et al* (2000) and therefore stated in the section of the response dealing with the mailing that the claims beneath the graph would be amended to ensure compliance. Implicit within this was that the claims would be amended, irrespective of the material on which they were to appear. Also of note was that the covering letter was bespoke to the mailing and certified as part of the same item, as indicated by the reference number. Indeed, in its complaint Johnson & Johnson acknowledged that GlaxoSmithKline Consumer Healthcare '…agreed to withdraw the items and confirmed that it would make corrections to address a number of our concerns…' and '…also agreed to stop using any similarly affected materials'. It was clear from these statements that Johnson & Johnson was in no doubt as to GlaxoSmithKline Consumer Healthcare's intended action and GlaxoSmithKline Consumer Healthcare was therefore unsure as to why Johnson & Johnson had included this point in its complaint.

Overall GlaxoSmithKline Consumer Healthcare accepted a breach of Clause 25 with respect to the undertaking given in Case AUTH/1253/11/10, to clearly state the patient population studied when making comparative craving relief claims between NiQuitin 21mg/24hr patches and Nicorette 15mg/16hr patches based on Shiffman *et al* (2000). GlaxoSmithKline Consumer Healthcare took this extremely seriously and the measures subsequently taken had been detailed in the covering letter. GlaxoSmithKline Consumer Healthcare refuted all other allegations made by Johnson & Johnson of breaches of Clauses 7.2, 7.3 and 25.

PANEL RULING

The Panel noted Johnson & Johnson's allegation that there was no evidence to suggest that the pattern of cravings and lapses in Shiffman *et al* (1997) applied to patients being treated with NRT. The Panel did not accept that Figure 1 in Shiffman and Ferguson provided *prima facie* support as suggested by GlaxoSmithKline Consumer Healthcare; it depicted placebo-controlled data. The study authors noted that smoking lapses commonly occurred in the evening and late night hours but the authors did not observe higher craving during these time periods. The authors noted that many studies had shown that smoking lapses were associated with acute increases in craving when smokers experienced provocative situations and thus the occurrence of such lapses during the evening and night hours might be due to exposure to such stimuli rather than to any inherent diurnal rhythm in the intensity of background craving. The Panel considered the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

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

The Panel noted that in Case AUTH/1401/12/02 it was alleged that the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' inferred a greater likelihood of success in smoking cessation with a 24-hour patch than with a 16-hour patch. The Appeal Board, *inter alia*, considered that the claim implied that because NiQuitin CQ was effective in relieving morning cravings, it would also be effective in long-term smoking cessation. The phrase 'from the word go' appeared to differentiate NiQuitin CQ from the 16-hour patches referred to in the preceding paragraph. The Appeal Board considered that the claim implied that NiQuitin CQ 24-hour patch was more likely to help a patient to stop smoking than a 16-hour patch. The Appeal Board considered that the claim overstated the data and was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2.

Turning to the present case, Case AUTH/2298/2/10, the Panel noted that there were some differences between the paragraph at issue and the claim considered previously. Nonetheless, the Panel considered that the claims at issue implied that as lapses were more likely to occur when morning cravings were elevated, the more effective protection against cravings afforded by the 24-hour patch meant that NiQuitin 21mg patch was more likely to help a patient stop smoking than a 16-hour patch. There was no evidence this was so. This impression was misleading, a breach of Clause 7.2 was ruled. Further this impression was contrary to the undertaking given in Case AUTH/1401/12/02 and thus a breach of Clause 25 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. Failure to comply with the undertaking in this instance bought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

4 Claim 'No other patch is proven more effective than NiQuitin 21mg Clear Patch at 4 or 52 weeks'

COMPLAINT

Johnson & Johnson noted that this claim in the letter was very similar to the claims about short- and long-term quit rates in the leaflet.

Johnson & Johnson alleged, as described above, that the claim implied superiority in terms of cessation rates for the NiQuitin 21mg patch over other patches. This was not the case and therefore Johnson & Johnson believed that this claim was in breach of Clauses 7.2 and 7.3.

RESPONSE

GlaxoSmithKline Consumer Healthcare did not specifically respond to this point.

PANEL RULING

The Panel considered that its rulings above at Points A4 and A6 were relevant here. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **23 February 2010**

Case completed **14 June 2010**

CASE AUTH/2299/2/10

SHIRE v FERRING

Promotion of Pentasa

Shire complained about the promotion of Pentasa (mesalazine) by Ferring. The items at issue were a 'power of five' booklet, an A4 sheet and an advertisement which were produced by Ferring Global solely for the Gastro 2009 Congress held in the UK in November 2009 and were no longer in use. Shire supplied Mezavant XL (mesalazine).

The detailed response from Ferring is given below.

Page 5 headed of the booklet headed'… UC remission rates in active disease' detailed the results of Marteau *et al* (2005) and featured a bar chart which showed improved remission rates with Pentasa sachets plus Pentasa enema vs Pentasa sachets plus placebo enema. Shire alleged that the claims 'Nearly 50% improvement in remission rate by adding Pentasa 1g enema' and 'Near normal mean quality of life achieved by 8 weeks and faster using Pentasa sachet + enema combination', did not represent the data and were unclear and misleading.

The Panel noted that the claim 'Nearly 50% improvement in remission rate by adding Pentasa 1g enema' was below a bar chart which showed a remission rate of 43% in patients treated with oral Pentasa plus placebo enema vs a 64% remission rate for those treated with oral Pentasa plus Pentasa enema. In that regard the Panel considered that it was clear that the claim meant that half as many patients again benefitted from treatment with Pentasa enema compared with those receiving a placebo enema. The Panel did not consider that the claim, in the context in which it appeared, was misleading as alleged. No breach of the Code was ruled.

The claim 'Near normal mean quality of life achieved by 8 weeks and faster using Pentasa sachet + enema combination' was referenced to Currie *et al* (2007). The authors stated that at eight weeks both arms of Marteau *et al* had, on average, almost normal quality of life compared to the UK standard population. The authors did not quantify the normal quality of life in the UK standard population. Quality of life was measured using the EQ-5D measure which had a range of zero (worst possible health state) to 1 (perfect health). The Panel could find no evidence that the 'normal goal' was set as 1 as submitted by Shire. The Panel noted Ferring's submission that the EQ-5D value found for the UK standard population was 0.86.

The Panel noted that Shire's complaint about the claim 'Near normal mean quality of life achieved by 8 weeks and faster using Pentasa sachet + enema combination' was based on its belief that a normal quality of life was an EQ-5D score of 1. In that regard Shire had noted that the Pentasa enema treatment group scored only 0.921 at 4 weeks and 0.922 at 8 weeks. Both scores were more than 0.03 less than 1; a change of 0.03 units in the EQ-5D score was regarded as a clinically meaningful change in health status. Given, however Ferring's submission that the EQ-5D value for the UK standard population was 0.86, the Panel noted that the treatment group had exceeded that at both 4 and 8 weeks. The Panel thus did not consider that the claim was misleading as alleged. No breach of the Code was ruled.

In relation to page 7 headed 'Pentasa once daily', Shire alleged that the sub-heading 'All Pentasa preparations are approved for once daily use' was inaccurate. The prescribing information stated that for sachets and tablets when used for active disease the medicine was to be taken between 2 and 4 times a day. Maintenance treatment for tablets and sachets was once daily. Enemas and suppositories were to be used once daily.

The Panel noted that the page was headed 'Pentasa once daily' and sub-headed 'All Pentasa presentations are approved for once daily use'. These claims were qualified in the bullet points below and in that regard Ferring, in inter-company company dialogue, stated that adequate clarification had been given such that there was no breach of the Code. The Panel noted that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like.

The Panel considered that the claims 'All Pentasa presentations are approved for once daily use' beneath the heading 'Pentasa once daily' were misleading as alleged. A breach of the Code was ruled.

Shire noted that the A4 sheet 'Worldwide markets where Pentasa is available for the treatment of Crohn's disease; listed the countries where Pentasa was licensed for both active and maintenance treatment of Crohn's disease. The UK SPC for Pentasa did not include the Crohn's disease indication. Prescribing information had not been included.

Shire referred to the supplementary information to the Code which included:

- **'promotional material for a medicine or indication that does not have a UK marketing authorization must be clearly and prominently labelled to that effect'**
- **'… it must be stated that registration conditions differ from country to country'.**

The A4 sheet did not state that Pentasa did not have a UK marketing authorization for Crohn's disease.

The Panel noted that the A4 sheet looked like promotional material. It was in the same style as 'the power of five' booklet considered above. The Pentasa product logo appeared in the bottom right hand corner together with the claims 'Efficacy', 'Compliance', 'Lifestyle', 'Support' and 'Experience'. The Panel considered that, although only provided on request, the A4 sheet was promotional material for Pentasa.

The sheet listed those countries in which Pentasa was licensed for active Crohn's disease or for the maintenance of Crohn's disease. The material did not, however, include a clear and prominent statement that it was not so licensed in the UK. A breach of the Code was ruled. With regard to the UK prescribing information, the supplementary information stated that it had to be readily available even though it would not refer to the unlicensed indication. In the Panel's view the UK prescribing information did not have to be on the A4 sheet itself. The UK prescribing information had been available on the stand in 'the power of five' booklet. The Panel ruled no breach in that regard.

In relation to the 'power of five' advertisement in the programme, Shire alleged that the adverse event statement was not sufficiently prominent as it was written in the same font as the rest of the paragraph in the bottom left-hand corner of the advertisement.

The Panel noted that the adverse event statement was the first statement in a block of text. Although the font size was smaller than other text on the advertisement, given that it was the only block of text on an advertisement with very little other text, the Panel considered that it was sufficiently prominent. No breach was ruled.

Shire Pharmaceuticals Limited complained about the promotion of Pentasa (mesalazine) by Ferring Pharmaceuticals Ltd. The items at issue were a booklet (ref PEN/011/11/09v2), an A4 sheet (no reference) and an advertisement (no reference). Ferring submitted that all three items were produced by Ferring Global solely for the international Gastro 2009 Congress held in November 2009 in London. The materials were no longer in use. Shire supplied Mezavant XL (mesalazine).

A 'the power of five' booklet (PEN/011/11/09v2)

This booklet was obtained from Ferring's stand at the congress.

1 Page 5 headed '… UC remission rates in active disease'

Page 5 detailed the results of Marteau *et al* (2005) and featured a bar chart which showed improved remission rates with Pentasa sachets plus Pentasa enema vs Pentasa sachets plus placebo enema.

COMPLAINT

Shire was concerned with the claims below the bar chart that illustrated the remission rates of 2g sachets of Pentasa. Ferring had not represented the data accurately from Marteau *et al* by using such claims as 'Nearly 50% improvement in remission rate by adding Pentasa 1g enema' and 'Near normal mean quality of life achieved by 8 weeks and faster using Pentasa sachet + enema combination', referenced to Currie *et al* (2007).

Ferring's response to clarify the 'Nearly 50% improvement …' claim was that as clearly presented on the same page, Marteau *et al* reported that the remission rate at 8 weeks in the group receiving Pentasa 1g enema was 64%, while the remission rate in the group receiving placebo enema was 43%. The improvement in remission rate by adding Pentasa 1g enema was therefore 64 – 43 = 21%/(43/100) = 48.8%. All the necessary figures to support this claim were on the same page.

Shire did not believe that Ferring's method of calculating this measurement was either clear or correct. As the figures were already percentages, multiplying them by 100 gave an erroneous figure. Moreover, the authors stated that the study did not recruit sufficient patients for the assumptions required in the statistical analysis. Shire alleged that the claim was thus unclear and misleading, in breach of Clause 7.2.

Ferring's defence for the claim 'Near normal quality of life …' was that Currie *et al* reported on quality of life (QoL) results from Marteau *et al*. The abstract stated: Rapid improvement in QoL was evident in both treatment arms at 2 weeks (oral mesalazine plus mesalazine enema: Delta = 0.079 [p<0.001]: and oral mesalazine plus placebo enema: Delta = 0.097 [p=0.03]). However, a near normal QoL was achieved more quickly in the oral mesalazine plus mesalazine enema arm, whereby the mean QoL at 4 weeks was 0.921 (sd 0.14), vs 0.859 (sd 0.17) units in the oral mesalazine plus placebo enema arm (p=0.034). At 8 weeks, substantial improvement in QoL was then evidenced in both arms, whereby both had, on average, almost normal QoL compared to the UK standard population (oral mesalazine plus mesalazine enema: mean = 0.922 [Delta from baseline = 0.15; p<0.001] and oral mesalazine plus placebo enema: mean =0.920 [Delta = 0.16: [p<0.001]). The authors concluded: Treatment with mesalazine resulted in improved QoL as measured using a validated and widely used measure (EQ-5D). Near normal mean QoL was achieved by 8 weeks but it was achieved much faster using a combination of oral plus enema mesalazine compared to oral treatment alone. Although both formulations of mesalazine were highly effective, based on patient reported QoL scores the combination treatment was more rapid and consequently should be offered as

first line therapy for patients with mild-to-moderate ulcerative colitis.

Shire stated that the complexity of Ferring's response indicated that the above statement required further clarification which was not evident in the booklet. The data suggested that both groups at 8 weeks had the same QoL parameters, therefore, stating that the Pentasa sachet and enema combination worked faster than the Pentasa sachet plus placebo was misleading.

The mean QoL at 4 weeks for oral mesalazine plus enema was 0.921 (ie assumed nearly normal) and the value for oral mesalazine plus placebo enema was 0.859 (presumed not to be nearly normal). This did not support the claim that combination treatment worked faster. Currie *et al* set 'normal goal' as 1 and a change of 0.03 was determined to be a clinically meaningful change in health status. Shire thus queried how it was possible that 0.921 (at 4 weeks) or even 0.922 at 8 weeks could be described as nearly normal. Both mean scores were at least 0.07 points off normal.

Additionally, Ferring's response also highlighted the results obtained were the authors' conclusion and the findings were not published in a peer-reviewed journal. The data had only been presented as a poster with no substantiation of the validity of the authors' conclusions.

Shire alleged that the lack of supporting evidence and clarification of methodology in obtaining 'near normal quality of life' on this page made the above claims ambiguous and misleading in breach of Clause 7.2.

Shire alleged that the claim '84% of patients were willing to take the sachet + enema combination treatment *in the future*' (emphasis added) was in breach of the spirit of the undertaking that Ferring signed post-arbitration. Ferring had not clarified that 84% of the respondents were willing to take the combination treatment during a relapse of ulcerative colitis and not for long term maintenance therapy. In addition, Marteau *et al* cited to substantiate the claim, asked patients if they would take combination therapy in the case of a relapse. The response was that 84% in the mesalazine enema and 85% in the placebo enema group were willing to take combination therapy in the future. These figures indicated that the placebo enema group were actually more willing to have the combination treatment than the active Pentasa enema group.

The ruling from an independent arbitrator on a similar matter was provided.

During inter-company dialogue Ferring claimed that the page in question related to relapses in active disease and had not alluded to maintenance treatment. Ferring had agreed to amend this claim in future to clarify this still further.

Shire believed that the claim, '84% of patients were willing to take the sachet + enema combination treatment in the future' was open to interpretation, Shire believed that it was misleading and breached Clause 7.2.

RESPONSE

Ferring disagreed with Shire that claims below the bar chart were unclear and ambiguous.

With regard to the claim 'Nearly 50% improvement in remission rate by adding Pentasa 1g enema', as clearly presented on the same page, Marteau *et al* reported that the remission rate at 8 weeks in the group receiving Pentasa 1g enema was 64%, while the remission rate in the group receiving placebo enema was 43%. The improvement in remission rate by adding Pentasa 1g enema was therefore 64 – 43 = 21%, which was 21/(43/100) = 48.8%. All the necessary figures to support this claim were on the same page.

Ferring would not use this claim without the supporting figures on the same page as this could lead to confusion as to whether this figure was an absolute or relative percentage. In the context of this page, this potential confusion was avoided.

With regard to the claim 'Near normal mean quality of life achieved by 8 weeks and faster using Pentasa sachet + enema', Currie *et al* reported on QoL results from Marteau *et al*. The abstract stated:

> 'Rapid improvement in QoL was evident in both treatment arms at 2 weeks (oral mesalazine plus mesalazine enema: Delta= 0.079 [p<0.001]; and oral mesalazine plus placebo enema: Delta= 0.097 [p=0.03]). However a near normal QoL was achieved more quickly in the oral mesalazine plus mesalazine enema arm, whereby the mean QoL at 4 weeks was 0.921 (sd 0.14), vs 0.859 (sd 0.17) units in the oral mesalazine plus placebo enema arm (p=0.034). At 8 weeks, substantial improvement in QoL was then evident in both arms, whereby both had, on average, almost normal QoL compared to the UK standard population (oral mesalazine plus mesalazine enema: mean = 0.922 [Delta from baseline= 0.15; p<0.001] and oral mesalazine plus placebo enema: mean = 0.920 [Delta = 0.16; [p<0.001]).'

The authors concluded:

> 'Treatment with mesalazine resulted in improved QoL as measured using a validated and widely used measure (EQ-5D). Near normal mean QoL was achieved by 8 weeks but it was achieved much faster using a combination of oral plus enema mesalazine compared to oral treatment alone. Although both formulations of mesalazine were highly effective, based on patient reported QoL scores the combination treatment was more rapid and consequently should be offered as first line therapy for patients with mild-to-moderate UC.'

This was further substantiated by the publication of this study in a peer-reviewed journal, which concluded:

> 'Including 1g mesalazine enemas with 4g oral mesalazine significantly improved HRQoL in patients with active ulcerative colitis.' (Connolly *et al* 2009).

Ferring acknowledged that QoL data were complex but believed that the claim was properly substantiated.

In response to a request from the Authority for further information, Ferring stated that the EQ-5D value found for the UK standard population was 0.86 based on work by Kind *et al* (1999), which was a survey of 3395 men and women aged 18 or over living in the UK.

The EQ-5D results presented in the poster by Currie *et al*, gave mean QoL values at 4 weeks of 0.921 in patients receiving Pentasa sachets plus enemas compared with 0.859 for patients receiving Pentasa sachets alone. By 8 weeks the QoL values had converged so that mean QoL values were 0.922 in patients receiving Pentasa sachets plus enemas compared with 0.920 for patients receiving Pentasa sachets alone. These results compared favourably with the UK population norm of 0.86 and supported the claim that near normal quality of life was achieved by 8 weeks, and faster in patients receiving combination treatment with Pentasa sachets plus enemas.

Ferring did not agree that either claim was in breach of Clause 7.2.

With regard to the claim '84% of patients were willing to take the sachet + enema combination treatment in the future', Shire had alleged a breach of undertaking of an inter-company agreement. Firstly, the undertaking from the earlier arbitration related to an ambiguity in the claim 'Pentasa combination treatment was highly acceptable to patients', and as a result of the arbitration process, Ferring agreed not to use, 'highly acceptable' in this context without appropriate clarification. Ferring did not agree that there had been a breach of this undertaking with Shire.

Marteau *et al* (2005) stated:

> 'Acceptability of combination therapy
> A total of 51/61 patients (84%) in the mesalazine enema and 45/53 patients (85%) in the placebo enema group were willing to take a combination therapy in the future.'

Ferring acknowledged that in this study patients were asked whether they would take combination therapy in the case of relapse. However, Ferring had not made any claim that the acceptability figure related to maintenance therapy and it should be noted that this page clearly related solely to relapses in active disease. Ferring did not agree with Shire that this claim was misleading, or that it was in breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim 'Nearly 50% improvement in remission rate by adding Pentasa 1g enema' was below a bar chart which showed a remission rate of 43% in patients treated with oral Pentasa plus placebo enema vs a 64% remission rate for those treated with oral Pentasa plus Pentasa enema. In that regard the Panel considered that it was clear that the claim meant that half as many patients again benefitted from treatment with Pentasa enema compared with those receiving a placebo enema. The Panel did not consider that the claim, in the context in which it appeared, was misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the claim 'Near normal mean quality of life achieved by 8 weeks and faster using Pentasa sachet + enema combination' was referenced to Currie *et al*. The authors stated that at eight weeks both arms of Marteau *et al* had, on average, almost normal quality of life compared to the UK standard population. The authors did not quantify the normal quality of life in the UK standard population. Quality of life was measured using the EQ-5D measure which had a range of zero (worst possible health state) to 1 (perfect health). The Panel could find no evidence in either Currie *et al* or Connolly *et al* that the 'normal goal' was set as 1 as submitted by Shire. The Panel noted Ferring's submission that the EQ-5D value found for the UK standard population was 0.86.

The Panel noted that Shire's complaint about the claim 'Near normal mean quality of life achieved by 8 weeks and faster using Pentasa sachet + enema combination' was based on its belief that a normal quality of life was an EQ-5D score of 1. In that regard Shire had noted that the Pentasa enema treatment group scored only 0.921 at 4 weeks and 0.922 at 8 weeks. Both scores were more than 0.03 less than 1; a change of 0.03 units in the EQ-5D score was regarded as a clinically meaningful change in health status. Given, however Ferring's submission that the EQ-5D value for the UK standard population was 0.86, the Panel noted that the treatment group had exceeded that at both 4 and 8 weeks. The Panel thus did not consider that the claim was misleading as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this part of the complaint the Panel noted that Currie *et al* reported that at four weeks the mean quality of life in the Pentasa sachet plus Pentasa enema combination arm was 0.921 vs 0.859 units in the Pentasa sachet plus placebo enema arm. In that regard the Panel considered that, compared with the UK standard population (EQ-5D value of 0.86 units), the Pentasa sachet plus placebo enema arm had achieved a near normal quality of life at four weeks and the

Pentasa sachet plus Pentasa enema arm had exceeded it at four weeks. The Panel was thus concerned that the claim 'Near normal mean quality of life achieved by 8 weeks and faster using Pentasa sachet and enema combination' was misleading given the four week data for both treatment groups and Ferring's submission that the normal EQ-5D score of the UK population was 0.86. The Panel requested that Ferring be advised of its views.

2 Page 7 headed 'Pentasa once daily'

COMPLAINT

Shire stated that the sub-heading 'All Pentasa preparations are approved for once daily use' was inaccurate. The prescribing information provided at the back of the booklet stated:

Sachets:	Active disease: up to 4g daily in 2-4 divided doses. Maintenance treatment: 2g once daily.
Tablets:	Active disease: up to 4g in 2-3 divided doses. Maintenance treatment: 2g once daily.
Enema:	Adults – one enema at bedtime.
Suppositories:	1 suppository daily.

There was a clear discrepancy between the claim and the Pentasa summaries of product characteristics (SPCs). There was no clear distinction between maintenance treatment (to which the claim applied) and active treatment of mild-to moderate ulcerative colitis.

During inter-company dialogue Ferring denied that the claim was inconsistent with Pentasa's SPC as used in the context of the page which included full details of the indications for which each Pentasa presentation could be used with a once daily dose.

The once daily claim and the SPCs for Pentasa sachets and tablets did not match. Shire disagreed that adequate qualification had been provided on this page, as the booklet contained both acute and maintenance data (page 5 was headed '… UC remission rates in active disease') thus readers would assume that the claim related to active disease and maintenance treatment. Hence Shire asserted that the manner in which this claim was currently portrayed was misleading and ambiguous in breach of Clause 7.2.

RESPONSE

Ferring stated that the sub-heading 'All Pentasa presentations are approved for once daily use' was not inaccurate, nor was it inconsistent with the Pentasa SPCs as used in the context of the page, which included full details of the indications for which each Pentasa presentation could be used with a once daily dose. It was true that Pentasa tablets and sachets had a once daily dose approved only for maintenance treatment, and this was clearly itemised below this claim. However, Pentasa suppositories and enema were approved for once daily dosing for both active disease and maintenance treatment. Ferring confirmed that this claim would not be used unless it was adequately clarified. As adequate clarification had been prominently provided on this page in the form of a comprehensive listing for each Pentasa formulation, Ferring did not agree with Shire's assertion that this page was in breach of Clause 7.2.

PANEL RULING

The Panel noted that the page was headed 'Pentasa once daily' and sub-headed 'All Pentasa presentations are approved for once daily use'. These claims were qualified in the bullet points below and in that regard Ferring, in its letter to Shire dated 18 December, stated that adequate clarification had been given such that there was no breach of the Code. The Panel noted, however, that it was a principle of the Code that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like as referred to in the supplementary information to Clause 7, General.

The Panel considered that the claims 'All Pentasa presentations are approved for once daily use' beneath the heading 'Pentasa once daily' were misleading as alleged. A breach of Clause 7.2 was ruled.

B A4 sheet – Worldwide markets where Pentasa is available for the treatment of Crohn's disease (no reference)

COMPLAINT

Shire noted that the A4 sheet listed the countries where Pentasa was licensed for both active and maintenance treatment of Crohn's disease. The UK SPC for Pentasa did not include the Crohn's disease indication.

The sheet lacked the required prescribing information as it contained an off-licence use/indication of Pentasa and both the brand name and a non-proprietary name of the medicine.

Ferring had responded stating that the sheet was available at its exhibition stand and, as required by the supplementary information to Clause 3, as it referred to unlicensed indications it could not be considered to be a promotional item and could not include UK prescribing information.

Shire noted that the supplementary information to Clause 3 included:

- '… in relation to an unlicensed indication, UK approved prescribing information must be readily available for a medicine authorized in the UK even though it will not refer to the unlicensed

indication …'
- 'promotional material for a medicine or indication that does not have a UK marketing authorization must be clearly and prominently labelled to that effect'
- '… it must be stated that registration conditions differ from country to country'.

The A4 sheet did not have prescribing information that was readily available, nor state that Pentasa did not have a UK marketing authorization for Crohn's disease.

Shire alleged a breach of Clause 3.

RESPONSE

Ferring confirmed that the sheet was available only on request at the stand as described in the supplementary information to Clause 3. As the sheet only listed countries where Pentasa was licensed for the treatment of Crohn's Disease it was not considered to be a promotional item for the UK and therefore did not include UK prescribing information. As a non-promotional piece, this item was not formally signed off in the UK, although Ferring UK staff provided guidance on its content. Ferring submitted that UK prescribing information was freely available on the stand. Ferring did not agree with Shire's assertion that the provision of this sheet on request was in breach of Clauses 3.2 or 4.1.

In response to a request for further information, Ferring submitted that although there was no promotional literature or exhibition panels that included information about the use of Pentasa in Crohn's disease, a significant proportion of delegates from Europe attended the meeting. Ferring believed it was appropriate to have a list of countries in which the indication for acute or maintenance treatment in Crohn's disease was approved to assist in discussions with these delegates should they wish to discuss these indications. As these discussions could take place at the exhibition stand, which would be a promotional setting in the UK, Ferring considered it appropriate to provide a sheet consistent with the supplementary information to Clause 3, which advised that the names of countries with authorizations for indications that were unlicensed in the UK should be available. This sheet was not visible on the stand and was available only on request.

PANEL RULING

The Panel noted that the A4 sheet had the appearance of promotional material. It was in the same style as 'the power of five' booklet considered above. The Pentasa product logo appeared in the bottom right hand corner together with the claims 'Efficacy', 'Compliance', 'Lifestyle', 'Support' and 'Experience'. The Panel considered that, although only provided on request, the A4 sheet was promotional material for Pentasa.

The sheet listed those countries in which Pentasa was licensed for active Crohn's disease or for the maintenance of Crohn's disease. The material did not, however, include a clear and prominent statement that it was not so licensed in the UK. A breach of Clause 3.2 was ruled. With regard to the UK prescribing information, the supplementary information stated that it had to be readily available even though it would not refer to the unlicensed indication. In the Panel's view the UK prescribing information did not have to be on the A4 sheet itself. The UK prescribing information had been available on the stand in 'the power of five' booklet. The Panel ruled no breach of Clause 3.2 in that regard.

The Panel noted that Ferring had referred to Clause 4.1. Whilst Shire had referred to the absence of prescribing information it did so in relation to the supplementary information to Clause 3 and did not cite Clause 4.1. There was no allegation of a breach of Clause 4.1 and so the Panel made no ruling in that regard.

C 'the power of five' advertisement in the Gastro 2009 programme (no reference)

COMPLAINT

Shire alleged that the adverse event statement was not sufficiently prominent as it was written in the same font as the rest of the paragraph in the bottom left-hand corner of the advertisement.

Shire alleged a breach of Clause 4.10.

RESPONSE

Ferring acknowledged that this item was in breach of Clause 5.6 as incomplete wording was used in this abbreviated advertisement, the statement omitted the final sentence, 'Adverse events should also be reported to Ferring Pharmaceuticals Ltd'.

PANEL RULING

The Panel noted that the adverse event statement was the first statement in a block of text. Although the font size was smaller than other text on the advertisement, given that it was the only block of text on an advertisement with very little other text, the Panel considered that it was sufficiently prominent. No breach of Clause 4.10 was ruled.

Complaint received **23 February 2010**

Case completed **25 May 2010**

CASE AUTH/2305/3/10

CLINICAL PHARMACIST v PFIZER

Menopause patient website

A clinical pharmacist complained that a website produced and sponsored by Wyeth, contained out dated information about the risks of hormone replacement therapy (HRT). In particular the data presented on the website indicated that oestrogen-only HRT was protective against breast cancer vs an increased risk presented in the more recent data contained in the BNF.

The complainant alleged that Wyeth had misrepresented the data and the website needed updating.

Wyeth had recently merged with Pfizer and so the matter was taken up with that company.

The detailed response from Pfizer is given below.

The Panel noted that the Wyeth website had been shut down as soon as Pfizer became aware of its content. The material at issue, provided by Pfizer, had been certified in April 2008 by Wyeth. The section of the website referring to breast cancer risk for oestrogen-only HRT in patients aged 50-59 and 60-69 was provided. The data was taken from the Women's Heath Initiative (WHI) Study (2004).

The data for each age group was presented as the number of women in a group of 1,000 who had never taken HRT who were at risk of breast cancer followed by another page showing how many would be as risk if all 1,000 women used oestrogen-only HRT for 5 years. The 50-59 age group background data was shown as a grid of 1,000 tiny figures of women with 21 figures highlighted and a very prominent '21' superimposed over the grid ie in a group of 1,000 women aged 50-59 who had never taken HRT, 21 would be at risk of developing breast cancer. Readers were asked how many would be at risk if they all used oestrogen-only HRT. The next screen ie the equivalent grid for 1,000 women aged 50-59 who had taken oestrogen-only HRT for five years had 15 tiny figures highlighted but had a very prominent '-6' superimposed over the grid. Less prominently, above the grid it was stated that 'If you were all using oestrogen-only HRT, then 15 of you would be at risk'. The prominent numbers shown on the equivalent grids for women aged 60-69 were '24' on the background grid and '-6' on the oestrogen-only HRT grid. The data had been taken from the WHI Study (2004) which assessed the affects of the most commonly used HRT in the US. The study authors had stated that the possible reduction in breast cancer risk required further investigation.

The Drug Safety Update of September 2007 (issued by the MHRA and the Commission on Human Medicines) reported the background incidence of breast cancer per 1,000 women in Europe aged 50-59 and 60-69 and noted that use of oestrogen-only HRT for 5 or 10 years was associated with an increased risk (2 additional cases in women aged 50-59 who took oestrogen-only HRT for 5 years and up to 9 additional cases in the 60-69 year old group who took oestrogen-only HRT for 10 years). It was further noted that European studies had generally identified higher breast cancer risk than US studies which might be due to differences in the prevalence of obesity. It was stated in the Drug Safety Update that the risk of breast cancer was increased in women who took HRT for several years; combined HRT was associated with the highest risk with a lower risk associated with oestrogen-only HRT. It was noted that some studies had not shown an increased risk with oestrogen-only HRT. The Drug Safety Update did not state or imply that oestrogen-only HRT might decrease the risk of breast cancer.

The Panel considered that it was unacceptable to refer only to 2004 US data and to not include 2007 European data on a UK website that was certified in 2008. It was extremely important that information given to patients about the long-term risks of therapy was fair, factual and not misleading. The website at issue claimed that there was less of a risk of developing breast cancer with the use of oestrogen-only HRT whereas other data reported either no difference in the risk or additional risk.

The Panel considered that the website was not based on an up-to-date evaluation of all the evidence. The use of very prominent minus numbers over the oestrogen-only HRT grids meant that the data that had been used was not presented in a balanced way; it exaggerated the differences in background incidence of breast cancer and the incidence in the oestrogen-only HRT groups. Breaches of the Code were ruled as acknowledged by Pfizer.

The Panel considered that high standards had not been maintained. A further breach of the Code was ruled.

A clinical pharmacist complained about a website produced and sponsored by Wyeth, www.menopausefacts.co.uk. Wyeth had recently merged with Pfizer Limited and so the matter was taken up with that company.

COMPLAINT

The complainant noted that the website at issue informed patients about the risks and benefits of hormone replacement therapy (HRT). References to

the Women's Health Initiative (WHI) Study and data from the Medicines and Healthcare products Regulatory Agency (MHRA)/Committee on the Safety of Medicines (CSM) dated from 2004 had both been superseded by the data in the Drug Safety Update of September 2007 as summarised in the British National Formulary (BNF), 58.

The data presented on the website therefore indicated that oestrogen-only HRT was protective against breast cancer vs an increased risk presented in the more recent data contained in the BNF.

The complainant alleged that Wyeth had misrepresented the data and the website needed to be updated.

When writing to Pfizer, the Authority asked it to consider the requirements of Clauses 7.2, 9.1 and 22.2 of the Code.

RESPONSE

Pfizer submitted that on its merger with Wyeth it had acquired a number of existing Wyeth projects of which the website at issue was one, it had now been shut down.

Pfizer acknowledged that before its closure some of the content required updating with regard to current UK clinical and regulatory opinion on HRT and the risk of breast cancer. The company thus accepted that there could potentially have been breaches of Clauses 7.2 and 22.2 of the Code. The website was closed down as soon as Pfizer became aware of the situation.

Pfizer considered it harsh to judge that it had not maintained high standards. Whilst it acknowledged that the balance of UK clinical opinion might now be that there was a small increased risk associated with the use of oestrogen-only HRT, there was no international consensus on the matter (2010 position statement of the North American Menopause Society). Indeed, even within the UK there were conflicting data and opinions (Roberts 2007). Therefore, bearing in mind the fluent nature of the clinical debate and that Pfizer had closed down the site as soon as it knew of its content, the company did not consider a ruling of a breach of Clause 9.1 was warranted.

In response to a request for further information Pfizer explained that in the WHI Study, women in the oestrogen-only arm demonstrated no increased risk of breast cancer after an average of 7.1 years of use, with six fewer cases of invasive breast cancer per 10,000 women per year of oestrogen-only use. This was not statistically significant, however the risk of breast cancer was statistically significantly reduced in three subgroups (50-59, 60-69 and 70-79yrs) upon post-hoc analysis where fewer breast cancers with localised disease were diagnosed in the oestrogen-only group compared with the placebo group (Hazard ratio, 0.69; 95%CI, 0.51-0.95).

The most recent Drug Safety Update, September 2007 stated that the risk of breast cancer was increased in women who took HRT for several years. It also mentioned that the risk of breast cancer was lower for those treated with oestrogen-only HRT than with combined HRT. The update further noted that some studies had not shown an increased breast cancer risk for oestrogen-only HRT and that the decision to prescribe HRT should be based on a thorough evaluation of the potential benefits and the potential risks of treatment.

Given that the website was discontinued as soon as Pfizer became aware of its content, which it acknowledged necessitated updating prior to its closure, as well as the differing clinical expert opinion and conflicting body of evidence requiring further research, Pfizer believed that high standards had been met and therefore a ruling of a breach of Clause 9.1 was not warranted.

PANEL RULING

The Panel noted that the Wyeth website had been shut down as soon as Pfizer became aware of its content. The material at issue, provided by Pfizer, had been certified in April 2008 by Wyeth. The section of the website referring to breast cancer risk for oestrogen-only HRT in patients aged 50-59 and 60-69 was provided. The data was taken from the WHI Study (2004).

The data for each age group was presented as the number of women in a group of 1,000 who had never taken HRT who were at risk of breast cancer followed by another page showing how many would be at risk if all 1,000 women used oestrogen-only HRT for 5 years. The 50-59 age group background data was shown as a grid of 1,000 tiny figures of women with 21 figures highlighted and a very prominent '21' superimposed over the grid ie in a group of 1,000 women aged 50-59 who had never taken HRT, 21 would be at risk of developing breast cancer. Readers were asked how many would be at risk if they all used oestrogen-only HRT. The next screen ie the equivalent grid for 1,000 women aged 50-59 who had taken oestrogen-only HRT for five years had 15 tiny figures highlighted but had a very prominent '-6' superimposed over the grid. Less prominently, above the grid it was stated that 'If you were all using oestrogen-only HRT, then 15 of you would be at risk'. The prominent numbers shown on the equivalent grids for women aged 60-69 were '24' on the background grid and '-6' on the oestrogen-only HRT grid. The data had been taken from the WHI Study (2004) which assessed the affects of the most commonly used HRT in the US. The study authors had stated that the possible reduction in breast cancer risk required further investigation.

The Drug Safety Update of September 2007 (issued by the MHRA and the Commission on Human Medicines) reported the background incidence of breast cancer per 1,000 women in Europe aged 50-

59 and 60-69 and noted that use of oestrogen-only HRT for 5 or 10 years was associated with an increased risk (2 additional cases in women aged 50-59 who took oestrogen-only HRT for 5 years and up to 9 additional cases in the 60-69 year old group who took oestrogen-only HRT for 10 years). It was further noted that European studies had generally identified higher breast cancer risk than US studies which might be due to differences in the prevalence of obesity. It was stated in the Drug Safety Update that the risk of breast cancer was increased in women who took HRT for several years; combined HRT was associated with the highest risk with a lower risk associated with oestrogen-only HRT. It was noted that some studies had not shown an increased risk with oestrogen-only HRT. The Drug Safety Update did not state or imply that oestrogen-only HRT might decrease the risk of breast cancer.

The Panel considered that it was unacceptable to refer only to 2004 US data and to not include 2007 European data on a UK website that was certified in 2008. It was extremely important that information given to patients about the long-term risks of therapy was fair, factual and not misleading. The website at issue claimed that there was less of a risk of developing breast cancer with the use of oestrogen-only HRT whereas other data reported either no difference in the risk or additional risk.

The Panel considered that the website was not based on an up-to-date evaluation of all the evidence. The use of very prominent minus numbers over the oestrogen-only HRT grids meant that the data that had been used was not presented in a balanced way; it exaggerated the differences in background incidence of breast cancer and the incidence in the oestrogen-only HRT groups. Breaches of Clauses 7.2 and 22.2 were ruled as acknowledged by Pfizer.

The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaint received **26 March 2010**

Case completed **19 May 2010**

PHARMACIST v PFIZER

Alleged promotion of unlicensed generic losartan

A pharmacist complained about a Pfizer commercial account manager who had discussed the price of losartan at a time when it was not available in generic format. The complainant asked if Pfizer had a licence for it and was told by the representative not yet, it was still in the application process.

The detailed response from Pfizer is given below.

The Panel noted that the complainant referred to a discussion with a named commercial account manager around the beginning of February. It appeared to be a face-to-face discussion in that the complainant stated that only the commercial account manager was present. Pfizer did not know the identity of the complainant. Pfizer acknowledged that the commercial account manager named by the complainant had discussed generic losartan before Pfizer received the relevant marketing authorization. This discussion, however was not with the complainant but with a named buyer. Pfizer stated that this was the only verbal discussion the commercial account manager in question had with any of his buyers. Following this conversation the commercial account manager had emailed the buyer Pfizer's price list.

The Panel noted that the Code defined promotion as any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription supply, sale or administration of its medicines. The Code listed exemptions to this definition including 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating for example to pack changes, adverse-reaction warnings, trade catalogues and price lists provided they include no product claims'.

The Panel noted that under the Code a price list for licensed medicines was not covered by the definition of promotion provided no product claims were included. The price list in question listed the price of losartan which was unlicensed at the time. The Panel also noted that the Code defined a representative as someone calling upon members of the health professions and administrative staff in relation to the promotion of medicines.

The Panel considered that it was not clear whether the commercial account managers were representatives as defined in the Code. It appeared from their job profile that their role went further than only talking about the price of medicines. The Panel noted from Pfizer's submission that the price list for current and forthcoming generic products was circulated to the commercial account managers on 1 February. This was emailed by the commercial account manager in question on 2 February to some of his buyers. One of the recipients identified by Pfizer was not the complainant. However the Panel noted from Pfizer's submission that the price list had been sent to a number of buyers.

The Panel did not agree with Pfizer's submission that the discussion of forthcoming medicines that were or would be available within the generic industry was an activity that fell outside the Code. In the Panel's view such a discussion was potentially subject to the Code although of course dealing with wholesalers might be different to discussions with health professionals and appropriate administrative staff.

The price list provided gave details such as pack sizes, PIP codes and costs for a number of Pfizer generic medicines including losartan. A branded version of losartan, Cozaar was available but not from Pfizer. In the Panel's view the price list emailed on 2 February could not take the benefit of the exemption to the definition of promotion as it included information about generic losartan which was not licensed. In that regard the Panel considered that if sent to health professionals or appropriate administrative staff, the price list was potentially subject to the Code and likely to be in breach.

The Panel noted the information provided by the parties. The accounts differed. A judgement had to be made on the available evidence including the fact that Pfizer did not know who the complainant was. The complainant had the burden of proving his complaint on the balance of probabilities. The Panel considered that although Pfizer acknowledged that it had provided a price list to buyers before it received the losartan marketing authorization, there was no evidence that it had been provided to the complainant. In any event, the complaint was about a specific interaction between the complainant and the named commercial account manager; the complainant had not referred to a price list. On the basis of the complaint, the Panel ruled no breach of the Code.

A pharmacist complained about the conduct of a commercial account manager from Pfizer Limited.

COMPLAINT

The complainant submitted that a commercial account manager had discussed the price of losartan in February, it was not even available in generic format. The complainant asked if Pfizer had a licence for it, the representative said not yet, it was still in the application process.

In response to a request for further information, the complainant stated that he could not remember the date in February – it was around the beginning of the month. Only the named commercial account manager was present.

The complainant acknowledged that other companies tended to discuss discounts prior to launch, but he assumed that was done knowing that they had a marketing authorization for those products.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 3.1, 9.1 and 15.2 of the Code.

RESPONSE

Pfizer stated that it had launched its generic portfolio in 2010; currently it had six generic medicines in its portfolio with a publicised commitment to increase this number during 2010 and 2011.

The commercial account manager (commercial account manager) role at Pfizer was not a sales representative role and the commercial account manager's main responsibility was to have trade discussions with potential buyers including discussions on discounts and price lists; they did not get involved in promotional conversations.

On 4 February 2010, in order to inform a potential purchaser of Pfizer's generic products, the commercial account manager had a factual discussion with a buyer (not a pharmacist) about the price list of Pfizer's generic portfolio; one of the medicines listed was losartan. Discussing forthcoming generic medicines that were or would be available in the near future was a common and acceptable trade practice within the generic pharmaceutical industry. In the UK, Pfizer was granted the marketing authorization four days later on 8 February for this product. No promotional activity occurred; this was purely a mention of the price of a forthcoming product. As such, Pfizer did not consider that this activity fell within the scope of the Code. The company thus denied a breach of Clauses 3.1, 9.1 and 15.2 of the Code.

Pfizer noted that the commercial account manager in question was very experienced and had passed the ABPI Medical Representatives Examination in 1992 when he was working for Pfizer in a sales role. A copy of his certificate was provided. The commercial account manager was highly trained and had more than ten years of account management and sales experience.

In response to a request for further information Pfizer stated that on 1 February Pfizer distributed the price list for its current and forthcoming generic products to the commercial account manager's. This price list was essential information provided to the commercial account manager's in advance in order for them to discuss the current prices and any discounts and deals being offered by Pfizer to buyers. On 2 February, the commercial account manager emailed this information to some of his buyers one of whom represented a regional pharmacy chain which held a wholesale pharmaceutical dealer's licence. A copy of the email and its attachments (including the aforementioned price list) was provided. The two letters attached to the email, which related to Pfizer's acquisition of Wyeth, were not relevant to this case but were provided for completeness.

On 4 February the buyer left the commercial account manager a voicemail asking for his call to be returned. When he returned the call he was asked if Pfizer had received a marketing authorization for losartan from the Medicines and Healthcare products Regulatory Agency (MHRA). The commercial account manager informed him that Pfizer had applied for the authorization and would receive it in the near future.

The above was the only verbal discussion that the commercial account manager had with any of his buyers about the losartan marketing authorization and this was why Pfizer assumed that the complaint might have originated from him. Unless the complainant revealed his identity Pfizer was not willing to share this response with him as it contained commercially sensitive price information.

As could be seen, the commercial account manager did not make any promotional claims regarding Pfizer's generic portfolio. The exchange was merely of factual information regarding the price of the product in question and the status of the marketing authorization. Clause 1.2 specifically stated that promotion did not include factual and informative announcements. Price lists were given as an example of materials that were excluded from the scope of the Code, provided they included no product claims. As such, the Code did not apply to this interaction and hence no breach of either Clause 3.1 or 9.1 occurred.

The commercial account manager was a very experienced account manager and had passed the ABPI Medical Representatives Examination. He was highly trained and worked in various roles at Pfizer for the last 10 years. The main responsibility of the commercial account manager was to ensure that appropriate trade discussions were held with buyers about Pfizer's product portfolio.

Part of the induction programme for a commercial account manager included a presentation about Quality Assurance and Compliance (a copy of the presentation was provided). This presentation catered for all roles within the Commercial Account Directorate and, as such, covered the three categories of interaction mentioned on slide 6; brand promotion, commercial discussion and market expansion. As stated above, the CAMs did not get involved in promotional conversations (brand promotion). Slides 7 and 8 demonstrated that the do's and don'ts were very clear and understood by the whole team.

Pfizer believed that the commercial account manager conducted his duties with professionalism and high standards according to his brief. He also informed his

line manager on the same day of the discussion with the buyer in question that some concerns and questions had been raised by his customer regarding the marketing authorization of losartan. This written feedback proved that the commercial manager had maintained high standards at all times and that Pfizer had not breached Clause 15.2.

To summarize, the discussion between the commercial account manager and a buyer was based purely on factual, informative matters, ie a discussion of Pfizer's generic medicine price list. Accordingly, Pfizer believed that it was not in breach of Clause 3.1. Pfizer also believed that the qualifications and experience of the CAM and the honesty and integrity under which he acted was evidence that Pfizer had not breached Clause 9.1 or Clause 15.2.

PANEL RULING

The Panel noted that the complainant referred to a discussion with a named commercial account manager around the beginning of February. It appeared to be a face-to-face discussion in that the complainant stated that only the commercial account manager was present. The complainant did not mention an email. Pfizer did not know the identity of the complainant. Pfizer acknowledged that the commercial account manager named by the complainant had discussed generic losartan before Pfizer received the relevant marketing authorization. This discussion, however was not with the complainant but with a named buyer. Pfizer stated that this was the only verbal discussion the commercial account manager in question had with any of his buyers. Following this conversation the commercial account manager had emailed the buyer a copy of Pfizer's price list.

The Panel noted that Clause 1.2 defined promotion as any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription supply, sale or administration of its medicines. The Code listed exemptions to this definition including 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating for example to pack changes, adverse-reaction warnings, trade catalogues and price lists provided they include no product claims'.

The Panel noted that under the Code a price list for licensed medicines was not covered by the definition of promotion provided no product claims were included. The price list in question listed the price of losartan which was unlicensed at the time.

The Panel noted that Clause 1.6 defined a representative as someone calling upon members of the health professions and administrative staff in relation to the promotion of medicines.

The Panel considered that it was not clear whether the commercial account manager's were representatives as defined in the Code. It appeared from their job profile that their role went further than only talking about the price of medicines. The commercial account manager job profile referred to business relationships, wholesale and retail accounts and supply chains etc. There was no reference to the clinical or technical aspects of any medicine. Slide 7 of the Quality Assurance and Compliance presentation for the commercial account directorate stated, *inter alia*, 'DO separate brand promotion activities and/or opportunities from market expansion activities and/or opportunities'. The Panel noted from Pfizer's submission that the price list for current and forthcoming generic products was circulated to the commercial account manager's on 1 February. This was emailed by the commercial account manager in question on 2 February to some of his buyers. One of the recipients identified by Pfizer was not the complainant. However the Panel noted from Pfizer's submission that the price list had been sent to a number of buyers.

The Panel did not agree with Pfizer's submission that the discussion of forthcoming medicines that were or would be available within the generic industry was an activity that fell outside the Code. In the Panel's view such a discussion was potentially subject to the Code although of course dealing with wholesalers might be different to discussions with health professionals and appropriate administrative staff.

The price list provided gave details such as pack sizes, PIP codes and costs for a number of Pfizer generic medicines including losartan. A branded version of losartan, Cozaar was available but not from Pfizer. In the Panel's view the price list emailed to buyers on 2 February could not take the benefit of the exemption to the definition of promotion as it included information about generic losartan which was not licensed. In that regard the Panel considered that if sent to health professionals or appropriate administrative staff, the price list was potentially subject to the Code and likely to be a breach of Clause 3.1.

Turning back to the facts of the case before it the Panel noted the information provided by the parties. The accounts differed. A judgement had to be made on the available evidence including the fact that Pfizer did not know who the complainant was. The complainant had the burden of proving his complaint on the balance of probabilities. The Panel considered that although Pfizer acknowledged that it had provided a price list to buyers before it received the losartan marketing authorization, there was no evidence that it had been provided to the complainant. In any event, the complaint was about a specific interaction between the complainant and the named commercial account manager; the complainant had not referred to a price list. On the basis of the complaint, the Panel ruled no breach of Clauses 3.1, 9.1 and 15.2.

Complaint received **29 March 2010**

Case completed **2 July 2010**

ANONYMOUS v ASTRAZENECA

Promotion of Seroquel

An anonymous complainant alleged that the content of an AstraZeneca meeting was misleading and promoted Seroquel (quetiapine) outwith its marketing authorization. Seroquel was licensed for the treatment of schizophrenia and bipolar disorder.

The subject of the meeting was 'Cognitive treatment of borderline personality disorder (BPD)'. The first part concerned the use of cognitive therapy but according to the complainant soon moved onto which medicine should be used, of which Seroquel was recommended as the medicine of choice. It was not implied or stated that Seroquel was unlicensed for this diagnosis. The complainant considered that this was a contrived attempt to draw attendance on one subject then manipulate the talk to the use of an unlicensed medicine therefore deliberately misleading the audience.

The detailed response from AstraZeneca is given below.

The Panel noted that the parties' account of the meeting in question differed. The complainant alleged that the meeting, held almost 6 months' previously, was about cognitive treatment of borderline personality disorder and included a recommendation that Seroquel was the medicine of choice. The complainant had stated that the meeting was held in the last week of October or the first week of November. AstraZeneca submitted that the only meeting it had sponsored at the named venue in October/November 2009 was held on 5 November. The meeting was about schizophrenia, in line with the Seroquel summary of product characteristics (SPC), and that borderline personality disorder was only referred to by the speaker in order to answer an unsolicited question from the audience.

The Panel was very concerned to note that AstraZeneca had not been able to provide copies of the invitation, agenda or slides used at the meeting. This was wholly unacceptable. In that regard the company had no record of the proceedings and thus had been unable to provide a robust response to the complaint. The meeting had been sponsored by AstraZeneca; the local representative had briefed the speaker. The company was thus responsible for the format and content of the meeting. In that regard the Panel disagreed with AstraZeneca's submission that the presentation was educational and thus did not require certification. This submission appeared to contradict AstraZeneca's speaker guidance document which stated that meetings organised by the sales force were classified as promotional. AstraZeneca was responsible for what the speaker said on its behalf and in the Panel's view his slides should have been certified. The meeting confirmation note given to the out-patient manager stated that the meeting would comprise a presentation on an AstraZeneca product in the management of schizophrenia. The form further stated that the meeting would last 50 minutes and a simple buffet would be provided.

The agenda for the meeting as recorded on the territory management system stated that the meeting title was 'Schizophrenia case study'. The meeting approval document on the territory management system referred to Seroquel, a schizophrenia case study, acute schizophrenia and schizophrenia in the community.

The Panel noted that AstraZeneca had provided accounts of the meeting from three of the attendees. When asked what the meeting was about one person stated that it was about schizophrenia and that they thought borderline personality disorder might have been mentioned. A second person stated that the meeting topic was the management of borderline personality disorder with psychotherapy; they could not remember anything being presented on schizophrenia and they further stated that quetiapine was not mentioned. A third person also stated that the meeting was about the management of borderline personality disorder; they did not think that schizophrenia was discussed. The third person thought that, in discussion with the audience, anti-psychotics were mentioned a little but were not the main focus. Neither the Panel nor AstraZeneca knew the complainant's identity.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The complainant had provided no material to support their allegation. Two of the three witness statements, provided by AstraZeneca, however, appeared to give some support to the complainant's allegation in that both attendees thought the meeting was about borderline personality disorder. However, when one was asked if quetiapine was mentioned they said 'No, it was just an educational talk'. The other attendee thought anti-psychotics were mentioned a little but were not the main focus. When asked more generally about any discussion about pharmacotherapy, the attendee stated 'From memory the "usual thing" that although nothing is licensed in personality disorder some medications exert some useful impact'. The Panel considered

that there was no evidence to show that AstraZeneca had promoted Seroquel outwith its marketing authorization as alleged. Taking all of the circumstances into account, the Panel did not consider that on the balance of probabilities Seroquel had been promoted for borderline personality disorder. No breach of the Code was ruled. The Panel further considered that although there appeared to be some confusion about the topic of the meeting, there was no evidence to show that delegates had been misled about Seroquel. No breach of the Code was ruled. The Panel did not consider that it had any evidence to show that the meeting was disguised promotion. No breach of the Code was ruled. Similarly the Panel considered that it had no evidence to show that the representative had not maintained a high standard of ethical conduct. No breach of the Code was ruled.

The Panel noted that AstraZeneca's record of the meeting was extremely limited. This was wholly unacceptable. The company did not know what invitations had been sent on its behalf, nor had it certified the presentation delivered. In the Panel's view this was extremely poor practice. The Panel was concerned that material that would have helped AstraZeneca respond to this complaint had either not been generated or copies had not been kept. This had left the company vulnerable and unable to robustly respond to the allegations made. Nonetheless the complaint at issue was about the content of the meeting, not the arrangements for it and in that regard there was no evidence to show that high standards had not been maintained. The Panel ruled no breach of the Code.

An anonymous complainant complained about the promotion of Seroquel (quetiapine) by AstraZeneca. Seroquel was licensed for the treatment of schizophrenia and bipolar disorder.

COMPLAINT

The complainant alleged that an AstraZeneca meeting was not only misleading in its content but also blatantly promoted Seroquel outwith its marketing authorization. The complainant considered that the underhand way this meeting was held brought the pharmaceutical industry into disrepute and further weakened confidence with NHS employees.

The complainant submitted that the meeting in question was held in the last week of October or the first week in November 2009 at a named venue. The meeting was facilitated by the local AstraZeneca representative. The subject was 'Cognitive treatment of borderline personality disorder (BPD)'. The first part of the talk concerned the use of cognitive therapy but soon moved onto which medicine should be used, of which Seroquel was recommended as the medicine of choice. At no point was it implied or stated that Seroquel was unlicensed for this diagnosis.

The complainant considered that this was a contrived attempt to draw attendance on one subject then manipulate the talk to the use of an unlicensed medicine therefore deliberately misleading the audience.

When writing to AstraZeneca the Authority asked it to respond with regard to the requirements of Clauses 2, 3.2, 7.2, 9.1, 12.1 and 15.2 of the Code.

RESPONSE

AstraZeneca acknowledged that a meeting had taken place at the named venue on 5 November 2009. It was an educational speaker meeting organized by the local representative with support and assistance from an NHS out-patient manager of a partnership NHS foundation trust who coordinated meetings between pharmaceutical companies and the doctors' diaries. The representative discussed the arrangements with the out-patient manager which included potential invitees. The representative then sent the out-patient manager a meeting confirmation note to confirm their discussion. The local NHS standard practice was that the out-patient manager populated a standard NHS meeting form with the relevant details of the meeting and then sent the invitation to those health professionals that they knew would educationally benefit from pharmaceutical company speaker meetings. AstraZeneca stated that its meeting records indicated that six general adult psychiatrists and one doctor on a GP rotation attended the meeting. Prior to the meeting the out-patient manager also sent a reminder to the attendees of the logistical details of the meeting and confirmed attendees.

AstraZeneca submitted that the venue was selected as it was conveniently located for the intended audience and had a private function room away from the public where the educational meeting was held.

The speaker was a general adult consultant psychiatrist. The representative asked him to present a schizophrenia case study entitled 'Management of Schizophrenia'. The representative visited the speaker three times and briefed him on the educational requirements of the meeting and the Code in line with the AstraZeneca Speaker Briefing Guidance document. The representative asked the speaker to discuss a real life schizophrenia patient case study with relevance to Seroquel, based on the speaker's experience as reflected in the meeting confirmation note. In response to this brief, the speaker prepared and presented an anonymised patient case study in schizophrenia and discussed the disease area and various treatment options, including Seroquel, which was the medicine used to manage the patient in question. The treatment of a patient with schizophrenia was in line with the marketing authorization and in accordance with the summary of product characteristics (SPC) for Seroquel. The

speaker was not briefed to discuss the use of Seroquel in patients with borderline personality disorder. Therefore, AstraZeneca denied a breach of Clause 3.2.

There was no evidence to suggest that the information presented in the case study was not factual, accurate or balanced or was misleading. Therefore, AstraZeneca did not believe there had been a breach of Clause 7.2.

The meeting started at 7.30pm and finished with questions and discussions at 8.45pm when an evening meal was served. Seven health professionals (including the speaker) and two AstraZeneca representatives attended.

During the presentation, one of the attendees asked the speaker an unsolicited question about borderline personality disorder and schizophrenia. The speaker answered the question using a separate presentation saved on his laptop which the AstraZeneca representative was unaware of. The speaker had created and used this presentation with his own medical team earlier that month. In the presentation he referred to guidance from the National Institute for Health and Clinical Excellence (NICE) in order to answer the question. In answering the question, the speaker stated that atypical anti-psychotics should not be used for borderline personality disorder. The question about borderline personality disorder was not solicited by either the speaker or the AstraZeneca representative. After answering the question the speaker returned to the agreed presentation to proceed with the talk. The second presentation was not planned by the speaker or AstraZeneca and was only used to effectively reply to a question from the audience. The content of the main presentation was educational and any reference to therapy areas that were outside the licence for Seroquel was as a legitimate, professional and independent response to an unsolicited question in that area. Therefore, AstraZeneca did not believe there had been a breach of Clauses 3.2 or 12.1.

The representative followed a local procedure adopted by the NHS for organising local speaker meetings. The representative had visited the speaker three times to brief him on the requirements of the meeting including Code requirements and had briefed the meeting organiser with a written agenda. Therefore, AstraZeneca did not believe there had been a breach of Clause 15.2.

The meeting was an educational meeting based on a real life case study of a patient with schizophrenia and treatment options. It was consistent with the Seroquel marketing authorization. The speaker's reference to borderline personality disorder was in direct response to an unsolicited question from the audience. This was not planned and as such the response was neither briefed by the representative nor encouraged and was only a very small proportion of the overall education supplied by the speaker. As detailed above, AstraZeneca did not believe there was a breach of Clauses 3.1, 12.1, 7.2 or 15.2. Therefore AstraZeneca did not believe that high standards had been compromised or that the industry had been brought into disrepute and therefore denied a breach of Clauses of 2 and 9.1.

The representative had passed the ABPI Medical Representatives Examination and all AstraZeneca internal codes and policies. AstraZeneca did not intend to apply for a licence for borderline personality disorder and correspondingly there were no representatives' briefing materials on this matter.

AstraZeneca noted that the presentation was created independently by the speaker in response to a briefing from the representative and as such was intended to be an educational presentation and therefore it did not require certification. The company was unable to provide a copy of the presentation as it was the speaker's own slide deck which had since been deleted.

In response to a request for further information AstraZeneca stated that it had requested copies of the invitation from the representative who organized the meeting, the out-patient manager as well as the presenter and attendees. However, due to the time delay between the meeting date and the complaint the company had not been able to obtain a copy of the invitation. The information AstraZeneca had on its territory management system was the meeting confirmation note and the template invitation. Copes of both were provided.

In response to a request for a written agenda used by the representative to brief the meeting organiser, AstraZeneca referred to the meeting confirmation note previously provided. AstraZeneca provided a copy of the agenda as recorded on the territory management system but could not confirm whether the latter was sent by the representative to the out-patient manager.

AstraZeneca submitted that no written communication took place between the parties involved. Speaker briefing meetings took place as detailed above.

It appeared that no materials or agendas were distributed at the meeting.

The meeting was approved by the representative's manager and a copy of the relevant entry to the territory management system was provided.

AstraZeneca provided witness accounts from three delegates, although since the meeting took place about six months' ago recollection of specific details was sparse. One delegate recollected the meeting focussed on a schizophrenia case where mention might have been made of borderline personality disorder. This account was in line with the account above. Another delegate recollected that the meeting concentrated on the management

of borderline personality disorder although did not remember Seroquel being recommended for borderline personality disorder. The third delegate remembered that the presenter had technical difficulties with his presentation so had to use a draft slide presentation. He stated the presentation focused on borderline personality disorder and that pharmacological treatments might have been discussed during the group discussion but any such discussion was not the primary purpose of the meeting and was not initiated by the representative or the presenter.

AstraZeneca stated that after such a period of time had elapsed between the meeting and the complaint being received, the parties involved had different recollections of the event. AstraZeneca referred to the documentation in the territory management system and to its comments above. It appeared that the meeting was developed to cover a case of a patient with schizophrenia rather than borderline personality disorder however, during the meeting it appeared that in order to answer a question the presenter switched to a presentation on borderline personality disorder.

AstraZeneca denied a breach of Clauses 2, 3.2, 7.2, 9.1, 12.1, and 15.2 of the Code. AstraZeneca took any complaint seriously and so was reviewing internal procedures to ensure that processes were as robust as they needed to be to withstand any future complaints of this nature.

PANEL RULING

The Panel noted that the parties' account of the meeting in question differed. The complainant had alleged that the meeting, held almost 6 months' previously, was about cognitive treatment of borderline personality disorder and included a recommendation that Seroquel was the medicine of choice. The complainant had stated that the meeting was held in the last week of October or the first week of November. AstraZeneca submitted that the only meeting it had sponsored at the named venue in October/November 2009 was one held on 5 November. The meeting was about schizophrenia, in line with the Seroquel SPC, and that borderline personality disorder was only referred to by the speaker in order to answer an unsolicited question from the audience. It was difficult to know what had happened at the meeting.

The Panel was very concerned to note that AstraZeneca had not been able to provide copies of the invitation, agenda or slides used at the meeting. This was wholly unacceptable. In that regard the company had no record of the proceedings and thus had been unable to provide a robust response to the complaint. The meeting had been sponsored by AstraZeneca; the local representative had briefed the speaker. The company was thus responsible for the format and content of the meeting. In that regard the Panel disagreed with AstraZeneca's submission that the presentation was educational and thus did not require certification. This submission appeared to contradict AstraZeneca's speaker guidance document which stated that meetings organised by the sales force were classified as promotional. AstraZeneca was responsible for what the speaker said on its behalf and in the Panel's view his slides should have been certified. The meeting confirmation note given to the out-patient manager stated that the meeting would comprise a presentation on an AstraZeneca product in the management of schizophrenia. The form further stated that the meeting would last 50 minutes and a simple buffet would be provided. The template invitation, however, (to be completed by the out-patient manager) referred to 'Dinner' and the acceptance/rejection form attached appeared to allow those accepting the invitation to state which starter, main course and dessert they would like.

The AstraZeneca Speaker Briefing Guidance document referred extensively to the requirements of the Code and stated that the main focus of any meeting organised by AstraZeneca sales teams must be within licence. Such a meeting was classified as promotional and no data on unlicensed products or unlicensed uses of licensed products might be presented. The agenda for the meeting as recorded on the territory management system stated that the meeting title was 'Schizophrenia case study'. The meeting approval document on the territory management system referred to Seroquel, a schizophrenia case study, acute schizophrenia and schizophrenia in the community.

The Panel noted that AstraZeneca had provided accounts of the meeting from three of the attendees. When asked what the meeting was about one person stated that it was about schizophrenia and that they thought borderline personality disorder might have been mentioned. A second person stated that the meeting topic was the management of borderline personality disorder with psychotherapy; they could not remember anything being presented on schizophrenia and they further stated that quetiapine was not mentioned. A third person also stated that the meeting was about the management of borderline personality disorder; they did not think that schizophrenia was discussed. The third person thought that, in discussion with the audience, anti-psychotics were mentioned a little but were not the main focus. Neither the Panel nor AstraZeneca knew the complainant's identity.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The complainant had provided no material to support their allegation. Two of the three witness statements, provided by AstraZeneca, however, appeared to give some support to the complainant's allegation in that both attendees thought the meeting was about borderline personality disorder. However, when one was asked if quetiapine was mentioned they said 'No, it was just an educational talk'. The other attendee thought anti-psychotics were mentioned a little but were not

the main focus. When asked more generally about any discussion about pharmacotherapy, the attendee stated 'From memory the "usual thing" that although nothing is licensed in personality disorder some medications exert some useful impact'. The Panel considered that there was no evidence to show that AstraZeneca had promoted Seroquel outwith its marketing authorization as alleged. Taking all of the circumstances into account, the Panel did not consider that on the balance of probabilities Seroquel had been promoted for borderline personality disorder. No breach of Clause 3.2 was ruled. The Panel further considered that although there appeared to be some confusion about the topic of the meeting, there was no evidence to show that delegates had been misled about Seroquel. No breach of Clause 7.2 was ruled. The Panel did not consider that it had any evidence to show that the meeting was disguised promotion. No breach of Clause 12.1 was ruled. Similarly the Panel considered that it had no evidence to show that the representative had not maintained a high standard of ethical conduct. No breach of Clause 15.2 was ruled.

The Panel noted that AstraZeneca's record of the meeting was extremely limited. This was wholly unacceptable. The company did not know what invitations had been sent on its behalf, nor had it certified the presentation delivered. In the Panel's view this was extremely poor practice. The Panel was concerned that material that would have helped AstraZeneca respond to this complaint had either not been generated or copies had not been kept. This had left the company vulnerable and unable to robustly respond to the allegations made. Nonetheless the complaint at issue was about the content of the meeting, not the arrangements for it and in that regard there was no evidence to show that high standards had not been maintained. The Panel ruled no breach of Clause 9.1.

The Panel noted its rulings above and considered that there could be no breach of Clause 2 of the Code. The Panel ruled accordingly.

Complaint received **15 April 2010**

Case completed **8 July 2010**

CASE AUTH/2313/4/10

TEVA v CHIESI

Clenil journal advertisement

Teva complained about a journal advertisement for Clenil (CFC-free beclometasone dipropionate (BDP) inhaler for asthma) issued by Chiesi. The advertisement was headed 'Life's full of disruptions. Changing to Clenil needn't be one of them' and featured a photograph of a cow which had apparently fallen through a ceiling to land on a desk which was littered with ceiling debris. 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' appeared in the bottom right hand corner of the advertisement next to a highlighted box which featured the product logo above the strapline 'CFC-free can be trouble-free'.

Teva alleged that the claims 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' and 'CFC-free can be trouble free' were all-embracing, unqualified, misleading, not capable of substantiation and exaggerated the benefits of Clenil.

The claims failed to take into account patient groups for whom switching to CFC-free would not be trouble-free for themselves or the health professional. In particular, Teva drew attention to those groups of patients who, on changing to Clenil, would have to start using a Volumatic spacer which they had not needed before.

Further the Clenil SPC detailed a theoretical potential for interaction in sensitive patients taking disulfiram or metronidazole. It also detailed other undesirable effects such as paradoxical bronchospasm, hypersensitivity reaction including rashes, urticaria, pruritus, erythema and angiodema and these too were included in the prescribing information which accompanied the advertisement. It also detailed the need to rinse the mouth immediately after inhalation to avoid candidiasis of the mouth and throat. This further supported Teva's view that Clenil was not 'trouble-free'.

Teva noted that in inter-company correspondence Chiesi had stated that 'By trouble trouble-free, we mean the least disruption to patients' care and medication whilst also causing the least disruption to the healthcare professional'. This recognised that Clenil was not 'trouble-free' by referring to 'least disruption' and not 'no disruption' as one would expect if it were 'trouble-free'.

Teva noted that it had requested substantiation for the claims and this was not forthcoming.

The detailed response from Chiesi is given below.

The Panel considered that the overall message of the advertisement was that changing to Clenil would be trouble-free. The Panel did not accept Chiesi's submission that the advertisement was a reminder of the topical issue of the disruption that might be encountered if a proactive approach to the transition to CFC-free inhalers was not taken. Nor did the Panel accept Chiesi's submission that the advertisement urged readers to consider using any CFC-free alternative and that it thus applied equally to Qvar. The advertisement at issue clearly promoted changing to Clenil and readers would associate the claims within only with that product.

The Panel noted Teva's submission about the potential difficulties of the transition to CFC-free Clenil. The Clenil SPC, stated that the Volumatic spacer must be used with certain doses in adults and irrespective of dose when administered to children and adolescents ≤15 years. The SPC also stated that patients who had difficulty in co-ordinating actuation and inspiration of breath should be told to use a Volumatic spacer to ensure proper administration. Chiesi had not responded on these points. The Panel considered that the transition from CFC-containing inhalers to Clenil was not as straightforward as implied by the absolute claim 'trouble-free'. The use of the word 'can' in the strapline 'CFC-free can be trouble-free' did not negate the impression that changing to CFC-free was trouble-free for everyone. The claims at issue 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' and 'CFC-free can be trouble free' were thus misleading, incapable of substantiation and all-embracing. Breaches of the Code were ruled. The Panel considered that given this ruling, the inference that a transition to Clenil from a CFC-containing inhaler was trouble-free for all patients was inconsistent with the terms of Clenil's marketing authorization; on changing to Clenil some patients would have to start using a Volumatic spacer which they had not had to do before on CFC-containing BDP. A breach of the Code was ruled.

The Panel noted that contrary to Chiesi's submission, Teva had clearly asked for substantiation of the two claims at issue. As substantiation had not been provided the Panel ruled a breach of the Code.

Teva UK Limited complained about a journal advertisement (ref CHCLE20100035) for Clenil (CFC-free beclometasone dipropionate (BDP) inhaler for asthma) issued by Chiesi Limited. Teva supplied Qvar (also a CFC-free BDP inhaler). Inter-company dialogue had failed to resolve the issues.

The advertisement was headed 'Life's full of

disruptions. Changing to Clenil needn't be one of them' and featured a photograph of a cow which had apparently fallen through a ceiling to land on a desk which was littered with ceiling debris. 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' appeared in the bottom right hand corner of the advertisement next to a highlighted box which featured the product logo above the strapline 'CFC-free can be trouble-free'.

COMPLAINT

Teva was concerned that the placement of the claims 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' and 'CFC-free can be trouble free' was such that both were associated with Clenil. Teva alleged that the claims were all-embracing, unqualified, misleading, not capable of substantiation and exaggerated the benefits of Clenil.

Importantly the advertisement did not refer to different patient types, such as those on high dose or under the age of 16 who would need to use a Volumatic spacer as stated in the Clenil summary of product characteristics (SPC).

The claims were not consistent with the SPC. They failed to take into account groups for whom switching to a CFC-free would cause more trouble to themselves and the health professional. These patient groups included those who might be on a breath-actuated inhaler or might need to use of a Volumatic (as stated in the Clenil SPC) that was not previously required with their CFC BDP.

The claim 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' was next to the Clenil logo and thus clearly associated with Clenil. There were major limitations to the use of Clenil as listed in its SPC. These would certainly not make the switch to Clenil 'trouble-free', would result in major inconvenience to the patient who would require additional training which would also inconvenience their health professionals.

Patients stabilised on CFC-containing BDP inhalers might receive and have been trained on different types of inhalers requiring different techniques. None of the CFC-containing BDP products required the use of spacers in patient groups identified in the Clenil SPC. The Clenil SPC stated that the following patients would need to use a Volumatic spacing device:

a) Patients who had difficulty synchronising actuation with inspiration with their inhaler.
b) Adults and adolescents ≥16 years of age taking total daily doses of ≥1000mcg BDP.
c) Children and adolescents ≤15 years of age, whatever the dose of BDP.

As above statements would have associated issues for patients and health professionals, Teva could not see how the use of Clenil could be deemed 'trouble-free'.

Further the Clenil SPC detailed a theoretical potential for interaction in sensitive patients taking disulfiram or metronidazole. It also detailed other undesirable effects such as paradoxical bronchospasm, hypersensitivity reaction including rashes, urticaria, pruritus, erythema and angiodema and these too were included in the prescribing information which accompanied the advertisement. It also detailed the need to rinse the mouth immediately after inhalation to avoid candidiasis of the mouth and throat. This further supported Teva's view that Clenil was not 'trouble-free'.

The claim 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' was purported to be substantiated by Chiesi in a letter by stating that 'By trouble trouble-free, we mean the least disruption to patients' care and medication whilst also causing the least disruption to the healthcare professional'.

Chiesi's own attempt to substantiate the claim in this letter recognised that Clenil was not 'trouble-free' by referring to 'least disruption' and not 'no disruption' as one would expect if it were 'trouble-free'. By stating least disruption, this recognised that there was a degree of disruption with Clenil which could not be associated with being trouble-free.

Teva alleged breaches of Clauses 7.2, 7.4, 7.10 and 3.2 of the Code.

Teva noted that it had requested substantiation for the claims and this was not forthcoming within the 10 day period allotted. In its response Chiesi made no attempt to provide substantiation. A breach of Clause 7.5 was alleged.

Teva requested a voluntary submission of this breach but this was not referred to in Chiesi's response despite a repeated request to answer all points during the teleconference and subsequent telephone call with Chiesi afterwards. Teva therefore requested that it was ruled that a subsequent breach of Clause 7.5 had been made in this instance in failing to substantiate as requested.

RESPONSE

Chiesi explained that 25 years ago scientists first alerted the world to the damage that CFC gases caused to the Antarctic ozone layer in the atmosphere. The ozone layer was crucial to life on earth as it shielded all life forms from the harmful UV radiation of the sun. As a result of this knowledge, there was widespread international consensus to ban the use of CFC gases and the Montreal Protocol treaty was first signed in 1987 to phase out the use of these harmful gases. Consequently, the global industrial production and use of CFC gases was sharply curtailed in the next

few years. However, it was deemed essential to continue to use CFC gases as propellants in inhalers for medicinal purposes until such time as suitable alternatives could be developed and manufactured on a sufficient scale. Over time, several pharmaceutical companies were able to do this successfully.

Over the past decade or so the transition from CFC-containing to CFC-free inhalers had taken place slowly in the UK and in a patchy geographical manner. These transitions had been handled with varying degrees of success, depending on the numbers of patients to be transitioned and the resources available to health professionals. The problem of transitioning patients from CFC-containing to CFC-free inhalers had occurred mainly where there had been large numbers of patients and little time to plan for these changes. This was borne out in 2003, when CFC-containing salbutamol inhalers were discontinued. As health professionals were not well prepared for this discontinuation, large numbers of patients were given prescriptions which their pharmacists could not fulfil because some pharmacies did not hold adequate stocks of CFC-free salbutamol inhalers whilst the CFC-containing versions had already been discontinued. Needless to say, the disruptions to patients, GPs and pharmacists were not only of a logistical nature but could have clinical significance, as these inhalers were needed to relieve the symptoms of early asthmatic attacks. It was in a similar context that the Clenil advertisement was run.

The last product in the UK to contain CFC-propellant delivered by a metered-dose inhaler was BDP which accounted for over 9 million units per annum in the UK (IMS data). Two CFC-free alternatives had been made available over the last few years in the UK ie Qvar (Teva) and Clenil (Chiesi). Since their launches, health professionals had been urged by both companies to consider a planned therapeutic transition to one of these two alternatives, in order to avoid disruptions to their patients and also to the daily running of their practices. If a therapeutic transition was planned and implemented in a timely manner, patients could quite easily be transitioned to a CFC-free alternative with a minimum of disruption.

Chiesi noted that in June 2009, Teva, wrote to all health professionals notifying them that it was going to discontinue CFC-containing BDP delivered via the Easi-breathe device from 30 September 2009; this gave health professionals three months in which to plan the transition of those patients on the Easi-Breathe device. In the same letter, Teva also stated that it expected stocks of its more widely used Beclazone (a CFC-containing BDP) metered-dose inhaler to be depleted during the first quarter of 2010.

Chiesi further noted that in January 2010, Teva wrote to wholesalers informing them that it would not supply any Beclazone metered-dose inhaler from 31 March 2010. This information was only sent to wholesalers and other relevant stakeholders and not sent directly to health professionals. A statement to health professionals from Teva was posted on its website on 7 February 2010.

On being made aware of the above letter to wholesalers, Chiesi began to run advertisements to highlight the fact that unless health professionals took immediate action to plan for therapeutic reviews and transition all their patients who were still receiving a CFC-containing BDP metered-dose inhaler to a CFC-free alternative, they and their patients could face disruptions to their practices and treatments respectively.

It was therefore within the above context of the imminent withdrawal of CFC-containing BDP inhalers and the need for health professionals to plan well ahead for the transition to CFC-free alternatives, that the Clenil advertisement at issue was run. The two claims, 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' and 'CFC-free can be trouble-free', were not directed to any one brand specifically but applied to all CFC-free BDP inhalers. As such, the claims simply urged health professionals to consider using any of the CFC-free alternatives which were currently available ie Qvar or Clenil.

Through the advertisement, Chiesi aimed to remind the reader of the window of opportunity to make the change to CFC-free BDP inhalers trouble-free, before CFC-containing BDP inhalers ran out of stock at the wholesalers and pharmacies. This clearly meant deciding to change patients proactively to a CFC-free alternative. The strapline 'CFC-free can be trouble-free' was valid when transitions were undertaken in a proactive manner. Clenil was a CFC-free alternative for adults and children with asthma and was available in the same range of devices and at the same dose regimens when transferring from a CFC-containing inhaler. Hence, the advertisement was seen as a reminder of the very topical issue of disruption that might be encountered if a proactive approach to transition was not taken.

Chiesi submitted that, with regard to patient safety, if repeat prescriptions of CFC-containing BDP inhalers were not changed in the immediate future to a CFC-free alternative, patients might be at risk of presenting pharmacist with prescriptions that could not be fulfilled when the former became unavailable. This would lead to the pharmacists ringing the patients' GPs and requesting urgently that they authorise changes of prescriptions there and then. Not only would this take up an inordinate amount of time by the pharmacists and the GPs, it might also confuse patients as they would be issued with a new inhaler without their prior knowledge. At the time of the advertisement, approximately 155,000 prescriptions still required a change and there was approximately only 8 weeks of CFC-containing product in the supply chain (IMS data).

In summary, the Clenil advertisement alerted health professionals of the imminent need to transition patients who were still on CFC-containing BDP inhalers to a CFC-free alternative. It focused on the clinical and logistical needs to make this transition proactively. Both Qvar and Clenil were available in the UK as suitable CFC-free alternatives. As such, the two claims at issue were not all embracing and not misleading. They were also not directed to any brand in particular and therefore it could not be alleged to be inconsistent with the Clenil SPC. Hence, Chiesi contended that the claims did not breach Clauses 7.2, 7.4, 7.10 and 3.2. Lastly, Clause 7.5 was not breached, as Chiesi was asked to provide substantiation on claims which it simply did not make in the advertisement, namely that it had disparaged Qvar and Teva; this was not possible when neither was mentioned in the advertisement.

PANEL RULING

The Panel considered that the overall message of the advertisement was that changing to Clenil would be trouble-free. The Panel did not accept Chiesi's submission that the advertisement was a reminder of the topical issue of the disruption that might be encountered if a proactive approach to the transition to CFC-free inhalers was not taken. Nor did the Panel accept Chiesi's submission that the advertisement urged readers to consider using any CFC-free alternative and that it thus applied equally to Qvar. The advertisement at issue clearly promoted changing to Clenil and readers would associate the claims within only with that product.

The Panel noted Teva's submission about the potential difficulties of the transition to CFC-free Clenil. Section 4.2 of the Clenil SPC, Posology and method of administration, stated that the Volumatic spacer must be used when Clenil was administered to adults and adolescents ≥16 years and taking total daily doses of ≥ 1000mcg and irrespective of dose when administered to children and adolescents ≤15 years. The SPC also stated that patients who had difficulty in co-ordinating actuation and inspiration of breath should be told to use a Volumatic spacer to ensure proper administration of the product. Chiesi had not responded on these points. The Panel considered that the transition from CFC-containing inhalers to Clenil was not as straightforward as implied by the absolute claim 'trouble-free'. The use of the word 'can' in the strapline 'CFC-free can be trouble-free' did not negate the impression that changing to CFC-free was trouble-free for everyone. The claims at issue 'Make the change to CFC-free beclometasone metered-dose inhalers trouble-free' and 'CFC-free can be trouble free' were thus misleading, incapable of substantiation and all-embracing. A breach of Clauses 7.2, 7.4 and 7.10 was ruled. The Panel considered that given this ruling, the inference that a transition to Clenil from a CFC-containing inhaler was trouble-free for all patients was inconsistent with the terms of Clenil's marketing authorization; on changing to Clenil some patients would have to start using a Volumatic spacer which they had not had to do before on CFC-containing BDP. A breach of Clause 3.2 was ruled.

The Panel noted that contrary to Chiesi's submission, Teva had clearly asked for substantiation of the two claims at issue. As substantiation had not been provided the Panel ruled a breach of Clause 7.5.

Complaint received **30 April 2010**

Case completed **15 June 2010**

ANONYMOUS EMPLOYEE v MERCK SERONO

Target contact rates

An anonymous, uncontactable key account manager complained that the target contact rates set verbally by his/her manager could not be achieved without breaching the Code.

The detailed response from Merck Serono is given below.

The Panel noted that the complainant had made a general allegation about target contact rates but had provided no details. The complainant had referred to verbal instructions given by his/her manager. The complainant had the burden of proving their complaint on the balance of probabilities.

The Panel noted that Merck Serono had provided documents to show that the objectives set for key account mangers related largely to sales targets not call rates. Key account managers were expected to contact a high percentage of individual health professionals within a three month period but it was not stated how many repeat calls had to be made. Merck Serono's customer recording management system showed that the estimated average annual call rate per key account manager (excluding service calls) was 2.4 with a variation of 0.8 to 4.5. Merck Serono currently could not distinguish calls from contacts on its customer recording management system although this would change shortly. The company estimated that currently 30% of recorded calls were service calls. The Panel noted that Merck Serono had calculated that although the estimated average annual call rate for all of its key account managers was 2.4, one member of the team had an estimated annual call rate of 4.5. Merck Serono must ensure that each individual team member complied with the Code, not just the team as a whole.

Nonetheless, the Panel considered that there was no evidence to support the complainant's allegation that the key account managers had been set target contact rates such that to achieve them they had to breach the Code. No breach of the Code was ruled.

COMPLAINT

The complainant stated that he/she was a key account manager who, together with colleagues, had been given a contact rate which forced them to initiate calls with customers at a frequency that breached the Code.

The complainant had been told that his/her performance would be measured on meeting this target. This contact rate target had been communicated verbally by the complainant's manager and not written down.

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

RESPONSE

Merck Serono provided a copy of its field force minimum standards, which it submitted made it clear what parameters were expected of its key account managers. The key account managers were largely briefed on sales targets rather than contact rates (a copy of a relevant action plan was provided). Merck Serono also provided a presentation (Rebif campaign brief) from which it submitted that the key account managers' objectives were determined and detailed coverage of customers expected.

Merck Serono submitted that data recorded on its customer recording management system showed that the call frequency rate per key account manager was 0.81/3 month period with a variation of 0.26 to 1.5 (a copy of the relevant document was provided), to include promotional and service calls. Merck Serono had not previously recorded objectively the different types of call but was moving to this new system shortly. A sample estimate from one of the teams showed that 30% of the calls were service calls. Therefore the estimated annual average call rate per key account manager was 2.4 with a variation of 0.8 to 4.5. Allowing for this approximate calculation the key account manager call rate was within the estimate of 3 promotional calls per year.

Merck Serono submitted that there had been no breach of Clauses 15.4 or 15.9 of the Code.

PANEL RULING

The Panel noted that the complainant was anonymous and uncontactable. The complainant had made a general allegation about target contact rates but had not provided any details. The complainant had referred to verbal instructions given to him/her by his/her manager. The complainant, who had the burden of proving their complaint on the balance of probabilities, could not be contacted for further information.

The Panel noted that Merck Serono had provided documents to show that the objectives set for key

account mangers related largely to sales targets not contact rates. Key account managers were expected to contact a high percentage of individual health professionals within a three month period but it was not stated how many repeat calls had to be made. Merck Serono's customer recording management system showed that the estimated average annual call rate per key account manager (excluding service calls) was 2.4 with a variation of 0.8 to 4.5.

The Panel noted that the supplementary information to Clause 15.4 of the Code stated, *inter alia*, that the number of calls made on a doctor or other prescriber by a representative each year should not normally exceed three on average. The supplementary information further stated that when briefing representatives companies should distinguish clearly between expected call rates and expected contact rates. Contacts included those at group meetings, visits requested by doctors or other prescribers, visits in response to specific enquiries and visits to follow-up adverse event reports. The Panel noted that Merck Serono currently could not distinguish calls from contacts on its customer recording management system although this would change shortly. The company estimated that currently 30% of recorded calls were service calls. The Panel noted that Merck Serono had calculated that although the estimated average annual call rate for all of its key account managers was 2.4, one member of the team had an estimated annual call rate of 4.5. Merck Serono must ensure that each individual team member complied with Clause 15.4 of the Code, not just the team as a whole.

Nonetheless, the Panel considered that there was no evidence to support the complainant's allegation that the key account managers had been set target contact rates such that to achieve them they had to breach the Code. No breach of Clauses 15.4 and 15.9 of the Code was ruled.

Complaint received **7 May 2010**

Case completed **1 June 2010**

CASE AUTH/2316/5/10

CONSULTANT IN PALLIATIVE MEDICINE v FLYNN PHARMA

Conduct of representative

A consultant in palliative medicine, complained about the conduct of a Flynn Pharma representative promoting Actiq (oral transmucosal fentanyl citrate). The complainant alleged that during a meeting in February the representative made false claims about Abstral [sublingual fentanyl citrate], marketed by ProStrakan; he claimed that Abstral was frequently swallowed and thus absorbed from the stomach rather than sublingually. This was neither an evidence-based statement nor true and in fact data showed Abstral had approximately 70% sublingual absorption/bioavailability. The complainant alleged that the representative also made inaccurate statements about the efficacy of Abstral.

The complainant stated that, in summary, the representative had claimed that with Actiq patients could 'turn their pain control on and off' by removing the Actiq lozenge once they achieved pain control. To the complainant's knowledge this was not evidence-based and the profile of the product did not lend itself to this. The complainant's main concern was the way the representative discussed Abstral. The representative discussed the lack of evidence for Abstral compared with Actiq which the complainant questioned.

The Authority informed the complainant that the claim that patients could 'turn their pain control on and off' with Actiq had been ruled in breach of the Code in Case AUTH/2303/3/10 and that the Director accordingly did not propose to take the matter up as a complaint. This was accepted by the complainant.

The detailed response from Flynn Pharma is given below.

The Panel noted that the complainant was concerned about what the representative had said about a competitor product, Abstral marketed by ProStrakan, in the course of promoting Actiq. Abstral was presented as a tablet for sublingual administration. The representative was reported to have stated, however, that Abstral was usually swallowed by patients and had poor bioavailability. The complainant submitted that there was no evidence to show that Abstral was swallowed and he noted that the bioavailability of Abstral was approximately 75% compared with 50% for Actiq.

The Panel noted that the Abstral summary of product characteristics (SPC) stated that the bioavailability of the product had not been studied but was estimated to be about 70%. The representative recalled telling the complainant that there was no clear published data to support the claim that Abstral's bioavailability was estimated to be 70%. According to his witness statement, it did not appear that the representative had told the complainant that the estimate of 70% was stated in the SPC. Although noting the lack of other published data the Panel nonetheless considered that the SPC contained the agreed details about a product and thus the fact that the information was included in that document gave it an official status. The SPC was a publicly available document. One slide from a presentation which Flynn used to brief its representatives about Abstral referred to the bioavailability of Actiq and Abstral and stated the 'Abstral SmPC states "The bioavailability of Abstral *has not been studied* but *is estimated* to be 70%" (how do they know – on what basis?)'. The Panel considered that by adding emphasis to the wording in the Abstral SPC and including the question 'How do they know – on what basis?', the training slide presentation disparaged Abstral. The Panel ruled a breach of the Code. In that regard the Panel considered that the briefing material would advocate a course of action which would be likely to lead to a breach of the Code. A breach of the Code was ruled.

With regard to the actual interview, the Panel noted that it was impossible to know what had transpired between the parties. The Panel noted that the complainant had generally alleged that the representative had made inaccurate statements about the efficacy of Abstral and that he had discussed the lack of evidence for Abstral compared with Actiq. No details had been provided by either party. However, given the content of the briefing material, that it appeared that the representative did not make it clear to the complainant that the estimated bioavailability of Abstral was stated in the SPC, that, according to his witness statement, the representative had appeared to question the speed of action and ease of use of Abstral and that the representative had finally advised the complainant to ask the Abstral representative for the bioavailability and efficacy data, the Panel considered that, on the balance of probabilities, the representative had misled the complainant about the competitor product. Breaches of the Code were ruled in this regard.

With regard to the allegation that the representative had stated that Abstral was usually swallowed by patients, the Panel noted that the representative had not specifically commented on it in his interview and when asked to by email three days later he stated that '… as the call was in excess of 3 months ago, unfortunately I don't have a sufficiently clear recollection to expand on the

information already provided'. The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. It was impossible to know what had transpired between the parties. Although noting that extreme dissatisfaction was usually required before an individual was moved to complain, on the basis of the information before it the Panel ruled no breach of the Code.

A consultant in palliative medicine complained about the conduct of a representative from Flynn Pharma Ltd, in relation to the promotion of Actiq (oral transmucosal fentanyl citrate).

COMPLAINT

The complainant noted that the representative visited him by appointment in February to discuss Actiq. The complainant alleged that during the meeting he made false claims about Abstral [sublingual fentanyl citrate], marketed by ProStrakan; he claimed that Abstral was frequently swallowed and thus absorbed from the stomach rather than sublingually. This was neither an evidence-based statement nor true and in fact data showed Abstral had approximately 70% sublingual absorption/bioavailability. The complainant alleged that the representative also made inaccurate statements about the efficacy of Abstral.

The complainant was concerned about the representative's professionalism on the day and had considered that his behaviour was unacceptable. The complainant had since been advised to report his concerns.

In further communication, the complainant stated that, in summary, the representative had claimed that with Actiq patients could 'turn their pain control on and off' by removing the Actiq lozenge once they achieved pain control. To the complainant's knowledge this was not evidence-based and the profile of the product did not lend itself to this. The complainant's main concern was the way the representative discussed Abstral. He provided false information about Abstral ie that it was usually swallowed by patients and had poor bioavailability when in fact the bioavailability of Abstral was much better than that of Actiq, approximately 75% compared with 50%, and there was no evidence to support his claim that the tablet was swallowed as it dissolved very fast sublingually. The representative also discussed the lack of evidence for Abstral compared with Actiq which the complainant questioned.

When writing to Flynn the Authority asked it to respond in relation to Clauses 7.2, 7.4, 8.1, 15.2 and 15.9 of the Code.

The Authority informed the complainant that the claim that patients could 'turn their pain control on and off' with Actiq had been ruled in breach of the Code in Case AUTH/2303/3/10 and that the Director accordingly did not propose to take the matter up as a complaint. This was accepted by the complainant.

RESPONSE

Flynn stated that it took all complaints seriously and none more so than when they were about a representative from a health professional. Whereas inter-company complaints might reflect a degree of competitive rivalry and positioning, in this case a health professional had felt the need to raise a matter not about promotional material content or claims, but more particularly, about professional conduct. Clearly there were implications in terms of company and individual reputation that might colour or influence a health professional's opinion about the individual, the company and the product(s).

Flynn noted that a senior manager had conducted a face-to-face interview with the representative in May. The record of that interview, signed by both parties, was provided. Clearly a little over three months had elapsed between the meeting with the complainant and the interview (and also the complaint itself) and the detail of the recollection of actual discussions and any interpretation of them needed to be viewed in that context. However, Flynn also provided a copy of the meeting record logged contemporaneously by the representative on the company's Customer Account Management system. Flynn submitted that there was nothing in either document which appeared inappropriate or gave rise to significant concerns.

The overall recollection was that the meeting went well as it resulted in the complainant providing contact information for other health professionals at the hospice.

The representative recalled that the discussion of Abstral was in response to the complainant stating that there were now a number of competitor products and that he was using Abstral. This was consistent with the representative's training insofar as Flynn's representatives were briefed not to proactively raise competitor products.

The representative made some remarks about Abstral in response to his understanding of an assertion that the product worked 'within a couple of minutes'. His response on this point was made with reference to the Abstral summary of product characteristics (SPC): significant pain relief from 15 minutes; no published data re bioavailability of Abstral; comment that Abstral took up to 30 minutes for complete absorption.

All of these points were consistent with the Abstral SPC as noted below.

Section 4.2, Posology and method of administration: 'If inadequate analgesia is not obtained within 15-30 minutes of administration of a single tablet, a second 100mcg sublingual tablet

may be administered'.

Section 5.1, Pharmacodynamic properties: 'Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes…'.

Section 5.2, Pharmacodynamic properties: 'Rapid absorption of fentanyl occurs over about 30 minutes following administration of Abstral. The bioavailability of Abstral has not been studied but is estimated to be about 70%.

Flynn submitted that given the representative's account of the meeting, his response was reasonable and measured and consistent with the Abstral SPC. Similarly, with respect to the view that a component of Abstral's absorption was via the oral route, this was consistent with the statement in Section 5.2 of the SPC.

Flynn stated that it would defend the representative's assertion about the estimate of Abstral's bioavailability at 70%. His comments were fundamentally matters of fact which Flynn did not consider were disparaging, misleading or incapable of substantiation and were offered as a relevant response to a point raised in discussion. Flynn submitted that this countered any potential breaches of Clauses 7.2, 7.4 and 8.1 of the Code. Flynn noted that the Abstral SPC stated that 'The bioavailability of Abstral has not been studied'. Indeed this was a specific point made in the technical briefing and training of Flynn's representatives as was indicated in the slide set and briefing notes provided. Flynn stated that to its knowledge, there were no specific published data which justified or clarified the bioavailability estimate for Abstral.

Flynn noted that with regard to the bioavailability of Abstral, the complainant had commented that it '… was much better than that of Actiq, approximately 75% compared with 50%,' and that 'data showed Abstral had approximately 70% sublingual absorption/bioavailability'. Given that there were no published studies setting out this position, these statements relied on the estimated 70% bioavailability reported in the Abstral SPC and/or separate unpublished comments and communications. The estimate of 50% bioavailability for Actiq came from Streisand *et al* (1991); approximately 25% came from the oromucosal absorption route and the other 25% resulted from oral absorption ie oral bioavailability was approximately 33%. Data from Streisand *et al* were given further credence by Darwish *et al* (2007) who reported the absolute and relative bioavailability of Actiq. In this study, the authors found an absolute bioavailability of 47% for Actiq and an oral bioavailability of 31% for fentanyl.

Flynn stated that if one took as a guide an assertion that the oral bioavailability of fentanyl was 33% (based on Streisand *et al*) and accepted the Abstral estimate of bioavailability as being 70%, then, to achieve this, would require that approximately 55% of the total dose of Abstral was absorbed through the oral mucosal route. If one also considered that a major benefit of the oral transmucosal delivery route for fentanyl was to achieve rapidity of (clinical) effect consistent with the temporal profile of a breakthrough pain episode, it was also reasonable to then assume that the substantial component of a product's clinical effect derived from the oromucosal absorption component of the dose.

It further seemed reasonable then that one would expect to see some correlation between the relative difference in oromucosal absorption for Actiq and Abstral and the optimum doses used in clinical trials (ie following titration) and ultimately then in the doses of the two products used in clinical practice. The available data, however, seemed to be inconsistent with this model.

Christie *et al* (1998) reported that 49% of patients did not require upward titration of Actiq from 200mcg and that 64% of patients required doses no higher than 400mcg. These proportions were very similar to those found in clinical practice as evidenced from the sales of Actiq by product strength (IMS data – not supplied) which suggested that the trial population was broadly representative of the patient population. However, the picture for Abstral was quite different – ProStrakan in Case AUTH/2207/2/09, reported that in trials, 48% of patients required doses of 600-800mcg. Flynn did not comment on the indicated Abstral dose based on IMS data as the data were more limited and confounded by the fact that for Abstral, a 'dose' was defined as one or two tablets (whereas for Actiq a dose was defined as a single lozenge).

Taking, however, the lower point of the dose range (600mcg), one was invited to accept that 48% of patients required a dose of (not less than) 600mcg. Although one must be cautious against making inferences in regard to pharmacokinetic-pharmacodynamic correlation, if the overall bioavailability of Actiq and Abstral were 50% and approximately 70% respectively and 64% of the patient population could be satisfactorily treated with doses of 200mcg or 400mcg Actiq, then it would follow that, the same population should be satisfactorily managed with doses of Abstral of ≤300mcg. If one applied the derived values for the oromucosal component of fentanyl absorption for Actiq and Abstral (of 25% and 55%, the latter figure being based on the 'estimate' of Abstral's overall bioavailability of 70% (ref SPC) and an oral bioavailability of 33% for fentanyl), and accepted that the oromucosal component contributed primarily to clinical effect, then Abstral doses of 100mcg or 200mcg would be expected to be comparable with Actiq doses of 200mcg or 400mcg. Although these arguments were somewhat theoretical, their logic was transparent and based on published data and estimates. Regardless, it was difficult on the available evidence, to reconcile the view as to Abstral's bioavailability with the trial

evidence that indicated that 48% of patients required a dose of ≤600mcg fentanyl, when Actiq trial and population data suggested a dose of 200mcg or 400mcg fentanyl was adequate to manage episodes of breakthrough cancer pain in 64% of cases.

With regard to the complainant's comments about '… [Abstral] was usually swallowed by patients and had poor bioavailability' and that 'Abstral was frequently swallowed and thus absorbed from the stomach rather than sublingually', the representative's witness statement did not address this matter and in response to a subsequent email, he was unable to recall any discussion or comment on his part in those terms. Flynn submitted that further insight was gleaned from review of its detailed briefing materials and accompanying training slide set. These were the only materials that had been briefed or supplied to Flynn's representatives about Abstral. They focussed largely on Rauck *et al* (2009) which was the only published clinical study describing Abstral. This was, however, notwithstanding that Flynn had, as yet, unresolved questions as to the formulation studied which were touched upon in a pending case, Case AUTH/2309/4/10. Regardless, the briefing document was, in Flynn's view, a balanced and entirely proper scientific analysis and critique of Rauck *et al*.

The training slide set largely followed the written briefing document. Flynn submitted that these materials provided an important reference point and refuted any suggested breach of Clause 15.9, it would be inappropriate to overly apply their teachings to a consideration of a discussion recalled and reported three months after it took place.

Flynn noted that the representative in question had a BSc in biotechnology and had worked in the pharmaceutical industry more or less continuously for 22 years. The representative joined Flynn in 2009 as part of a field-force expansion and took on representative responsibilities for Actiq in October 2009 pursuant to a commercial agreement between Cephalon and Flynn regarding UK sales and marketing responsibilities for Actiq. The representative had passed his ABPI examination.

Flynn stated that there was little doubt that the representative was highly experienced and appropriately qualified. This was the first complaint about his professional conduct in a 22-year career in pharmaceutical sales and marketing and he was understandably concerned and upset to be the subject of complaint. His career experience, unblemished record and personal integrity should, and did, feature in Flynn's assessment and response to the particulars of this case.

With regard to a potential breach of Clause 15.2 (high standards and professional conduct) Flynn submitted that its difficulty was the 'evidence' in considering this point and, indeed, any case where it turned on a discussion. However, to the extent that the complainant had felt cause to register a complaint, there was an 'issue' and this was something Flynn wished to resolve. Therefore, the company's position was, simply, that if the complainant genuinely felt after reviewing the above that there was 'unacceptable behaviour', then Flynn would consider accepting a ruling of a breach of Clause 15.2. Irrespective of the abovementioned arguments and the good character and record of the representative, who Flynn considered acted professionally and with good and proper intent, if offence had been caused the company would accept that at face value and without dispute.

PANEL RULING

The Panel noted that Flynn had agreed for its response to be sent to the complainant for comment before the Panel made its ruling. The Panel, however, considered that in this case such action was not necessary and it made its ruling based on the initial submissions by both parties.

The Panel noted that the complainant was concerned about what the representative had said about a competitor product, Abstral marketed by ProStrakan, in the course of promoting Actiq. Abstral was presented as a tablet for sublingual administration. The representative was reported to have stated, however, that Abstral was usually swallowed by patients and had poor bioavailability. The complainant submitted that there was no evidence to show that Abstral was swallowed and he noted that the bioavailability of Abstral was approximately 75% compared with 50% for Actiq.

The Panel noted that the Abstral SPC stated that the bioavailability of the product had not been studied but was estimated to be about 70%. The representative recalled telling the complainant that there was no clear published data to support the claim that Abstral's bioavailability was estimated to be 70%. According to his witness statement, it did not appear that the representative had told the complainant that the estimate of 70% was stated in the SPC. Although noting the lack of other published data the Panel nonetheless considered that the SPC contained the agreed details about a product and thus the fact that the information was included in that document gave it an official status. The SPC was a publicly available document. In a training slide presentation which Flynn used to brief its representatives about Abstral, slide 16 referred to the bioavailability of Actiq and Abstral. The statement about Abstral read 'Abstral SmPC states "The bioavailability of Abstral ***has not been studied*** but ***is estimated*** to be 70%" (how do they know – on what basis?)'. The Panel considered that by adding emphasis to the wording in the Abstral SPC and including the question 'How do they know – on what basis?', the training slide presentation disparaged Abstral. The Panel ruled a breach of Clause 8.1. In that regard the Panel considered that the briefing material would advocate a course of action which would be likely to lead to a breach of

the Code. A breach of Clause 15.9 was ruled.

With regard to the actual interview, the Panel noted that it was impossible to know what had transpired between the parties. The Panel noted that the complainant had generally alleged that the representative had made inaccurate statements about the efficacy of Abstral and that he had discussed the lack of evidence for Abstral compared with Actiq. No details had been provided by either party. However, given the content of the briefing material, that it appeared that the representative did not make it clear to the complainant that the estimated bioavailability of Abstral was stated in the SPC, that, according to his witness statement, the representative had appeared to question the speed of action and ease of use of Abstral and that the representative had finally advised the complainant to ask the Abstral representative for the bioavailability and efficacy data, the Panel considered that, on the balance of probabilities, the representative had misled the complainant about the competitor product. Breaches of Clauses 7.2 and 15.2 were ruled in this regard.

With regard to the allegation that the representative had stated that Abstral was usually swallowed by patients, the Panel noted that the representative had not specifically commented on it in his interview and when asked to by email three days later he stated that '… as the call was in excess of 3 months ago, unfortunately I don't have a sufficiently clear recollection to expand on the information already provided'. The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. It was impossible to know what had transpired between the parties. Although noting that extreme dissatisfaction was usually required before an individual was moved to complain, on the basis of the information before it the Panel ruled no breach of Clauses 7.2 and 7.4 of the Code.

During its consideration of this matter the Panel noted that slide 11 of the training slide presentation was headed 'Protocol Violations or Withdrawal of Consent. The slide, *inter alia*, stated that the study protocol in Rauck *et al* was difficult to adhere to because the tablet had to be placed 'under tongue in deepest part of the oral cavity and allow to dissolve, **without chewing sucking or swallowing the medication**'. The Panel noted that the competitor briefing document which detailed the findings of Rauck *et al* stated that one hypothesis for protocol violation or withdrawal of consent was that the '… study protocol was difficult to adhere to – if, for example patients were asked not to swallow for up to ten minutes to ensure effective sublingual absorption'. The Panel could not find this instruction anywhere in the published paper. The published paper stated that patients were instructed not to chew, suck or swallow the medication. It thus appeared from the briefing documents that difficulty in using the tablets was a major reason for protocol violation. The Panel, however, noted that although Rauck *et al* reported that a number of patients were withdrawn from the study due to 'protocol violation', no reasons for the violations were given. The Abstral SPC stated in Section 5.2 that Abstral was a quick dissolving sublingual tablet formulation. Rapid absorption of fentanyl occurred over about 30 minutes following administration. Rauck *et al* stated that sublingual fentanyl might provide additional benefits to patients as it was a small discreet tablet that did not require a delivery device or patient manipulation once it had been placed under the tongue; however, the impact of these properties had not been evaluated in a real-life setting. The Panel considered that the training slide and briefing document disparaged Abstral; they implied that patients would find the tablets difficult to take properly but there was no data to support this. The Panel requested that Flynn be advised of its concerns in this regard.

The Panel noted that the competitor briefing document under the heading 'Limitations of the Study' put forward a number of hypotheses to explain the reasons for protocol violation or withdrawal of consent from Rauck *et al* including 'To reduce the number of patients withdrawing from the study because of lack of efficacy or adverse events'. The Panel considered that the reasons put forward were conjecture on Flynn's part and in that regard disparaged Abstral. The Panel requested that Flynn be advised of its concerns in this regard.

Complaint received **7 May 2010**

Case completed **1 July 2010**

ANONYMOUS v GLAXOSMITHKLINE

Arrangements for a meeting

An anonymous, non-contactable complainant complained about a meeting held one Saturday morning in March 2010 at a luxury golf and spa resort hotel, sponsored by GlaxoSmithKline.

The complainant considered that the location, timing and venue were the factors which persuaded doctors to attend. Pharmaceutical companies should not use such tactics to entice doctors to their meetings. The event lasted only until lunchtime, after which the attendees could use the venue's extensive spa and golf facilities or visit local attractions.

The detailed response from GlaxoSmithKline is given below.

The Panel noted the meeting in question has been organised by an independent education provider for GPs and practice nurses. GlaxoSmithKline was one of the sponsoring companies. Two local hospital consultants each gave a one and a half hour presentation, mid morning coffee and lunch were provided and delegates were encouraged to visit the exhibition stands. The venue was stated as the name of the hotel only – there was no reference to golf or spa facilities.

The Panel noted GlaxoSmithKline's submission that it had paid for an exhibition stand and that no additional hotel facilities were endorsed or paid for by GlaxoSmithKline or the conference organisers. GlaxoSmithKline had not provided free or subsidised access to local attractions.

The Panel considered that delegates to the meeting had been invited on the basis of the educational/ scientific content which would be the attraction to attend rather than the venue and hospitality. The Panel considered high standards had been maintained. No breaches of the Code were ruled including Clause 2.

An anonymous, non-contactable complainant complained about arrangements for a meeting sponsored by GlaxoSmithKline UK Ltd.

COMPLAINT

The complainant noted that the meeting at issue had been held one Saturday, in March 2010 at a luxury golf and spa resort hotel.

The complainant considered that the location, timing and venue were the factors which persuaded doctors to attend. Pharmaceutical companies should not use such tactics to entice doctors to their meetings. The event lasted only until lunchtime, after which the attendees could use the venue's extensive spa and golf facilities, or visit local attractions.

The complainant considered that if the meeting arrangements were generally known, the public would be appalled.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

GlaxoSmithKline explained that the meeting at issue was an ENT [ear, nose and throat] and Paediatric Allergy Masterclass organised by an independent primary care education provider. The masterclass was a free study morning for GPs and practice nurses as part of a health education series which was run independently by the education provider. A certificate for 3 hours of continuing professional development (CPD) points was awarded to the health professionals that attended the event.

The content of these educational events was entirely run by the education provider, with no input by the sponsoring companies. All logistics, including registering the attendees for the event, were organised by the education provider.

The education provider invited pharmaceutical companies to sponsor its educational events and in return provided an exhibition area for sponsors. The sponsorship of the masterclass was clearly stated on the event flyer and the day programme (copies of both were provided). GlaxoSmithKline submitted that it had paid for an exhibition stand at the event. The masterclass in question was also sponsored by sixteen other pharmaceutical companies. The agenda for the meeting was included on the day programme, which also detailed the corporate sponsors. The course was provided free of charge to delegates which, as the day programme stated, would not be possible without the support of the sponsors.

The masterclass included a basic cold lunch and coffee. No other hotel facilities were endorsed or paid for by the education provider; this had been confirmed by the conference director. GlaxoSmithKline did not provide free or subsidised access to any of the hotel's facilities or surrounding attractions. Therefore, GlaxoSmithKline did not consider that this constituted a breach of Clause 19.1 of the Code. In addition, the event flyer

described the venue by the name of the hotel chain and not as a golf and spa resort.

GlaxoSmithKline did not consider that its sponsorship of the masterclass was in breach of Clauses 2, 9.1 or 19.1 of the Code. GPs and practice nurses were attracted to the masterclass because it was a high-quality, free educational event provided by two local consultants and not because of the location or venue.

PANEL RULING

The Panel noted that the meeting in question had been organised by an independent primary care education provider for GPs and practice nurses. That the masterclass was free of charge to practising GPs and practice nurses was as a result of pharmaceutical company sponsorship. According to the booking form a nominal fee would be charged to other health professionals. GlaxoSmithKline was one of seventeen companies to sponsor the event.

The masterclass was given by two local hospital consultants. The programme started at 9am with coffee and registration. From 9.30-11am one of the consultants gave a presentation on common ENT problems in general practice. After a half hour coffee and exhibition break the second consultant gave another one and a half hour presentation on the management of paediatric allergy in primary care. From 1-1.30pm delegates could have lunch and visit the exhibition. The booking form clearly stated that a free basic cold lunch would be provided. The venue was stated as the name of the hotel chain only – there was no reference to golf or spa facilities.

The Panel noted GlaxoSmithKline's submission that it had paid for an exhibition stand but had not provided free or subsidised access to any of the hotel's facilities or surrounding attractions. No additional hotel facilities were endorsed or paid for by the conference organisers.

The Panel considered that delegates to the meeting had been invited on the basis of the educational/ scientific content, which would be the attraction to attend rather than the venue and hospitality. The Panel ruled no breach of Clause 19.1. The Panel considered high standards had been maintained and ruled no breach of Clause 9.1.

The Panel noted its rulings above and considered that there could be no breach of Clause 2 of the Code; neither the event nor GlaxoSmithKline's involvement in it had brought discredit upon or reduced confidence in the industry. The Panel ruled accordingly.

Complaint received **28 May 2010**

Case completed **23 June 2010**

CODE OF PRACTICE REVIEW – AUGUST 2010

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

2235/5/09	**Cephalon/Director v Prostrakan**	**Promotion of Abstral**	**Breaches Clauses 2, 3.2, 7.2, 9.1 and 25.** **Audit required by Appeal Board** **Re-audit required by Appeal Board**	**Report from Panel to Appeal Board**	**Page 3**
2294/1/10, 2296/1/10 and 2297/1/10	**Journalist, Member of the Public and Ex-employee v AstraZeneca**	**Promotion of Seroquel**	**2294/1/10 – Breaches Clauses 7.2, 7.4 and 7.9** **2296/1/10 and 2297/1/10 – 7.2, 7.4, 7.9 and 9.1**	**Appeal by complainant (2297/1/10)**	**Page 9**
2295/1/10	**Hospital Chief Pharmacist v Cephalon**	**Supply of Effentora**	**Breaches Clauses 2, 9.1 and 15.2**	**Appeal by respondent**	**Page 16**
2298/2/10	**Johnson & Johnson/ Director v GlaxoSmithKline Consumer Healthcare**	**NiQuitin 21mg Clear Patch mailing**	**Two breaches Clause 2 Seven breaches Clause 7.2 Three breaches Clause 7.3 Two breaches Clauses 9.1 and 25**	**No appeal**	**Page 25**
2299/2/10	**Shire v Ferring**	**Promotion of Pentasa**	**Breaches Clauses 3.2 and 7.2**	**No appeal**	**Page 48**
2305/3/10	**Clinical Pharmacist v Wyeth**	**Menopause patient website**	**Breaches Clauses 7.2, 9.1 and 22.2**	**No appeal**	**Page 54**
2306/3/10	Pharmacist v Pfizer	Alleged promotion of unlicensed generic losartan	No breach	No appeal	Page 57
2311/4/10	Anonymous v AstraZeneca	Promotion of Seroquel	No breach	No appeal	Page 60
2313/4/10	**Teva v Chiesi**	**Clenil journal advertisement**	**Breaches Clauses 3.2, 7.2, 7.4, 7.5 and 7.10**	**No appeal**	**Page 65**
2315/5/10	Anonymous v Merck Serono	Target contact rates	No breach	No appeal	Page 69
2316/5/10	**Consultant in Palliative Medicine v Flynn Pharma**	**Conduct of representative**	**Breaches Clauses 7.2, 8.1, 15.2 and 15.9**	**No appeal**	**Page 71**
2323/5/10	Anonymous v GlaxoSmithKline	Arrangements for a meeting	No breach	No appeal	Page 76

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.